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STUDIES ON MEASLES

IV. RESULTS FOLLOWING INOCULATION OF CHILDREN WITH EGG-PASSAGE MEASLES VIRUS

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INTRODUCTION

A PREVIOUS report[1] reviewed studies concerning the inoculation of thirty-five supposedly susceptible children with active egg-passage measles virus[2] and five children with presumably inactive measles virus. The present report reviews and extends these observations over an additional 215 children and also thirty-seven controls exposed to the inoculated children. The report also includes consideration of the nature of the inoculum, the method of inoculation, and the results obtained in these children following such injections.

It has been demonstrated on three separate occasions[1] that the inoculation of susceptible children and monkeys with portions of the same blood from patients with active cases of measles in the early stages has resulted in measles typical for both species. The incubation period has been approximately the same, and some of the signs and symptoms of the disease have been quite similar in both man and monkey, although somewhat milder in the latter. Furthermore, continued use of the susceptible *Macaca mulatta* for determining by injection the activity of egg-passage virus used for inoculating children has demonstrated conclusively through ninety-one passages a typical but mild measles syndrome in the monkey which has almost its precise counterpart in the child injected with the same material. In the monkey, the most important observation made in so far as it was related to the human disease was the fact that animals which had suffered the mild disease characteristic of simian measles were no longer susceptible to second attacks of the

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disease.* This was true whether the recovered animals were injected by various routes with material from human beings with active cases of measles or with the egg-passage measles virus.

Of the 40 children inoculated with egg-passage virus who have already been described,[1] 5 received material which may well have been inactive due to repeated freezing and thawing during temperature changes in the refrigerator in which the material was stored. Of the remaining 35 children who were injected with active virus, 4 had very mild measles and 6 had coryza with or without leucopenia and questionable Koplik spots, so that approximately 29 per cent gave some evidence of measles. However, in this group of 35, the injected children in the New Jersey institutions, numbering 28, were older than those studied later in Philadelphia, and possibly, since the history of measles from parents of the older children in institutions is frequently incorrect, complete dependence for a negative history of measles should be placed only upon the Philadelphia children who had been followed from birth by the staff of the Children's Hospital. Since as mentioned, 5 children of the Philadelphia group of 12 were inoculated with material which was probably inactive, it seems of considerable significance that of the remaining 7 children, 4 gave evidence of reactions, whereas of the 28 New Jersey institutional children, there were but 6, or 21 per cent, who showed any reaction following inoculation with the active egg-passage virus.

These results have increased the doubts concerning the accuracy of the history in some of the older children who entered the institutions after early childhood. In view of these findings, it has appeared essential for the more accurate evaluation of the total data to divide the inoculated children into two groups: (a) those whose medical histories had been accurately followed from birth by physicians interested in the studies; (b) those whose medical histories from birth could be obtained only from the parents. Such a division has been justified by the results obtained in the additional groups to be reported here. There are also other factors which cannot as yet be fully evaluated but which may have influenced the results of the earlier experiments, such as potency and amount of the virus inoculum and the method of inoculation. These may be responsible for the positive reactions following inoculation of the Philadelphia children in the group of forty previously reported, since they were injected at a time when the technique of cultivating the virus on the chorioallantois and storing it for extended periods had been more fully mastered.

CLINICAL MATERIAL

A. Children Whose Medical Histories Had Been Accurately Followed From Birth by Physicians (184).—These children should be considered

*A single strain of virus, H. D., produced typical mild measles in Monkey 89. This animal, when it was inoculated later with a different strain of virus, contracted simian measles.

as approximately 100 per cent susceptibles. Those included in this category came from three sources:

1. Children who had been followed from birth in an outpatient study at the Children's Hospital, being seen routinely once a month by a physician on the staff of the hospital and twice a month by a graduate nurse. There were twelve in this group. Written permission was obtained from both parents of these children, and the procedure was thoroughly explained to them. The children were examined physically before inoculation and as far as possible were kept isolated in their homes following inoculation and until such time as all signs and symptoms of the reactions had disappeared. Such isolation was not always strict, owing to the congestion of the city districts in which the families resided and to the lack of discipline and care shown at times by the parents. Assurance was obtained as far as possible, both from the Department of Public Health of the city and from local physicians and neighbors that measles was not present in the city district where the family lived. Also, a time was chosen for such inoculation when measles was not epidemic in the city.

2. Nine children who were followed from birth in an orphanage under careful supervision. These children were isolated in a special isolation pavilion and the same precautions as already mentioned were taken, with greater success in this case.

3. Children who in almost every instance had been born and reared in a foundling hospital, the mothers remaining for temporary periods. The age range of those studied ran from 6 months to 4 years. All of these children, numbering 163, were supervised daily by both physicians and nurses. Permission for inoculation was obtained from parents or guardians. The children were all examined physically before the inoculations were performed, and, if severe infections were present in the group, no inoculations were attempted. In a hospitalized group of this age at almost any time of year, except possibly midsummer, one or two are apt to have coryza or evidences of a slight upper respiratory infection. Certain of these children (thirty-seven in all) with mild signs and symptoms were not inoculated but were permitted to remain with the other children as contact controls. There were no cases of other communicable diseases on the same floors at the time of inoculations, and, except for the personnel engaged in the studies, visitors were prohibited from entering the wards occupied by the inoculated children.

B. Children Whose Medical Histories From Birth Depended Wholly or in Part Upon the Parents (71).—Many children in this category were susceptible, but, despite all efforts to obtain accurate information from parents and in some cases physicians, the histories, though negative as obtained, may have been occasionally faulty. In this group, twenty-eight were previously reported,[1] and an additional forty-three are reported now. This group contains a large portion of the children in the earlier studies for three reasons:

1. It was difficult to obtain permission for inoculation of very young children followed from birth by physicians until the parents and

guardians could be assured that the procedure had been previously well tested on a moderate number of older children without harm to the children and with at least some possibility of success.

2. The parents of older children in large, well-equipped institutions with excellent medical personnel were accustomed to accepting the advice of the physicians in charge concerning studies of immunization procedures. The successful results which had previously been obtained[1] in the active immunization of monkeys afforded a satisfactory background for the encouragement of parents and guardians.

3. For the same reason it was possible in such institutions to obtain permission from the parents and guardians for challenge inoculations of the previously vaccinated children, which was regarded as an essential requirement in the early studies. These children were mostly resident in large New Jersey State institutions where hospital isolation facilities are excellent. In two groups in which an orphanage was used, the inoculated children were first separated from the other children by renting a summer home in a community many miles from the orphanage. The two groups from this orphanage were thus isolated at different intervals. These children were inoculated at a time when no epidemic diseases were prevalent in their vicinity and were examined physically in order to eliminate those with respiratory infections or other conditions which would contraindicate their use in the studies.

MATERIALS AND METHODS

The material used for inoculation was similar to that described previously,[1] namely, measles virus obtained from the body fluids of children with active measles and propagated for varying numbers of passages on the chorioallantois of the developing chick embryo.[2] It was either kept frozen or was desiccated from the frozen state. In each case, prior to its use in children, samples were inoculated into laboratory animals and artificial culture media in order to insure its freedom from other pathogenic agents, and as often as monkeys were available, a portion of the same material inoculated into each group of children was injected into a susceptible *Macaca mulatta* for purposes of control. For some groups of children manifesting reactions typical of mild measles following inoculation with a given lot of the egg-passage measles virus, therefore, there was a corresponding control monkey demonstrating simian measles.

Inoculations in children were carried out by the following routes:

1. *Intranasal.* In the earlier studies the intranasal drip method was used. One cubic centimeter of the egg-passage virus material was dripped into each nostril from a sterile pipette with the child in a recumbent position.

2. *Inhalation.* In the later studies, approximately 1 c.c. of the virus suspension was atomized directly beneath the child's nose into a cellophane shower cap covering the child's head. A small, electrically driven

pump provided the force behind the atomizer which ejected a barely visible fog containing no large droplets. By this method the material was inhaled deep into the respiratory tract.

3. *Subcutaneous.* Five children were inoculated by the subcutaneous route only and two by both the subcutaneous and intranasal routes.

4. *Intradermal.* In most of the children in whom this route was used, the material was injected into the skin of the upper arm on the outer aspect or into the skin of the anterior forearm in amounts of 0.2 to 1 c.c. into the chosen site. In various groups of children the intradermal inoculum, which consisted of dilutions of the original virus material from 1:10 up to 1:10,000, varied as to the number of the egg passages from the third to the sixty-sixth.

The children were examined previous to their injection for the purpose of detecting clinical disease and in order to differentiate any subsequent signs or symptoms from those already present at the beginning of the study. Except in a few instances, they were also examined daily, following inoculation, for Koplik spots, exanthem, conjunctivitis, coryza, cervical adenopathy, cough, temperature elevation, and malaise. The rectal temperature was taken two to three times daily unless elevation occurred, in which case it was taken four to six times in each twenty-four-hour period.

CLASSIFICATION OF REACTIONS TO INOCULATIONS

The evidence of measles following inoculation with egg-passage virus has been classified as follows:

1. Moderate (See Fig. 1)	Mild malaise Elevation of temperature (rectal) to 102° F. or higher Nasopharyngitis Rare cough Conjunctivitis, usually with photophobia Koplik spots Typical rash present but not usually florid
2. Mild (See Fig. 2)	Slight or no malaise Temperature from 100.8° F. (rectal) to 101.8° F. (rectal) Mild nasopharyngitis Conjunctivitis, usually without photophobia Koplik spots Typical light rash
3. Minimal (See Fig. 3)	No malaise No temperature elevation or under 100.8° F. (rectal) Very mild nasopharyngitis Slight conjunctivitis Koplik spots Typical light rash
4. Doubtful	Same as minimal or even mild but absence of definite Koplik spots
5. No positive evidence	No characteristic signs or symptoms

The moderate reactions have resembled closely measles against which convalescent or pooled adult serum has given almost complete protection. The essential evidence for this statement is the almost com-

plete absence of cough and the presence of only mild malaise in the vaccinated children. It is for this reason that the foregoing classification of the reactions need contain no term of greater severity than mod-

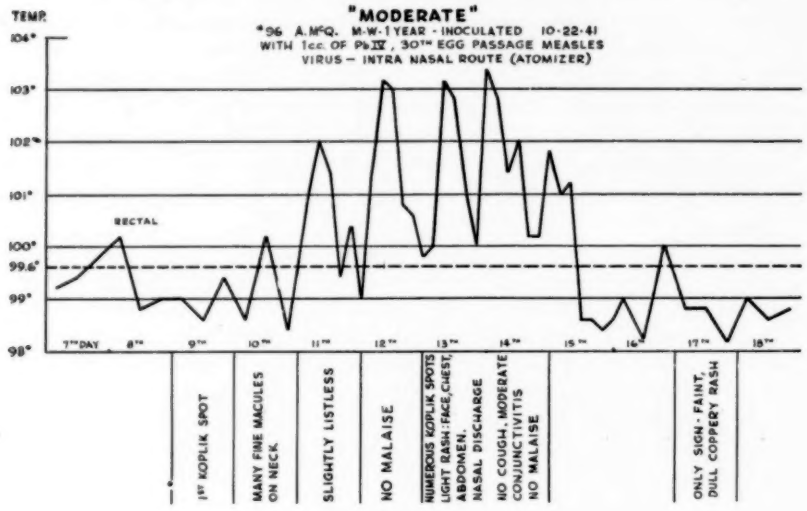

Fig. 1.

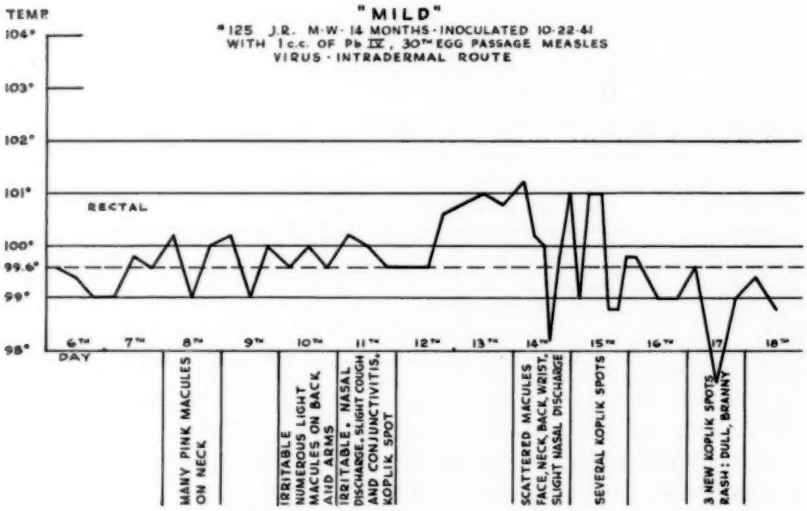

Fig. 2.

erate. Even with a temperature of 103° F. or over the fever has not been a sustained one, and the children have been brighter, more active, and far less toxic than is usual in measles.

Although most of the children could be grouped easily among the types of reactions outlined in the foregoing classification, a few cases did not fall accurately into any single class. This is best illustrated by the cases classified as doubtful in Table I, which analyzes the results of inoculation in children whose medical histories depended upon physicians. Among the doubtful group of forty-one children, there were at least thirty-two whose reactions were typical of the other children with positive reactions except for the absence of characteristic Koplik spots. Most of these thirty-two children had erythematous, blotchy, or hemorrhagic areas on the buccal mucosa at approximately the time Koplik spots were expected to appear. It is highly probable in these cases that

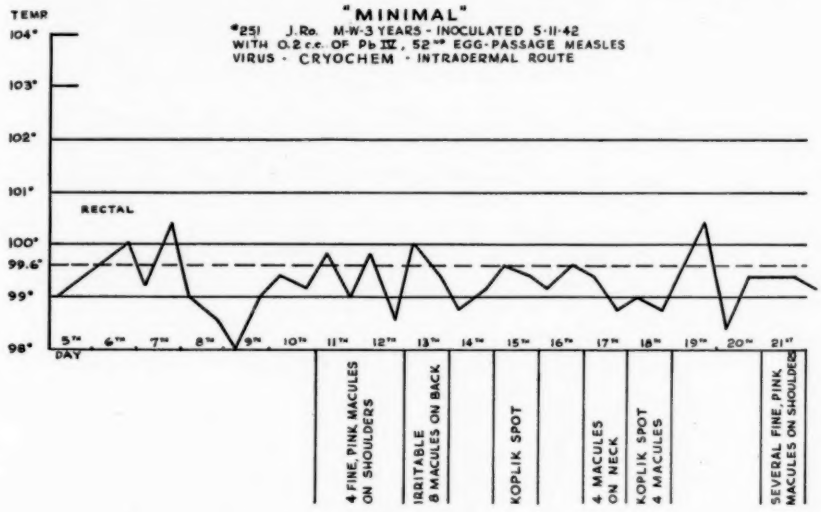

Fig. 3.

Koplik spots were present at some time during the period of their reactions, since a number of these children, during the critical period when Koplik spots were expected, were not examined by any of the authors for forty-eight hours. This may be compared with the common experience of the medical practitioner who frequently notes the appearance and disappearance of Koplik spots within a short period of time in addition to erythematous and hemorrhagic areas on the mucosa either before or after the occurrence of Koplik spots.

Among the entire group classified in Table I, when the three groups of moderate, mild, and minimal reactions are included, 137 children, or over 74 per cent, showed Koplik spots. If the thirty-two cases just described are also included with the 137 children showing Koplik spots, which appears to be justifiable, the positive measles reactions to egg-passage virus in this group of children reach 92 per cent.

Whereas the cough was infrequent even in those children showing moderate reactions, the amount of rash also gave little indication of the

TABLE I

RESULTS OF INOCULATION OF ACTIVE EGG-PASSAGE MEASLES VIRUS IN CHILDREN WHOSE MEDICAL HISTORIES DEPENDED UPON PHYSICIANS (INCLUDING 12 CHILDREN PREVIOUSLY REPORTED)

INSTITUTION, GROUP, AND DATE OF INOCULATION	NUMBER INOCULATED	VIRUS INOCULUM						CLASSIFICATION OF RESPONSE				
		STRAIN	PASSAGE (EGG)	FROZEN OR DRIED	DILUTION	AMOUNT (C.C.)	ROUTE	MODERATE	MILD	MINIMAL	DOUBTFUL	NO POSITIVE EVIDENCE
E. S. 1/30/40	1	H-D	4th	Frozen	Undil.	4 aa 2	IN SC	1				
Philadelphia I 3/4/40	6	P-V	9th	Frozen	Undil.	1 to 2	IN	1		1	1	3
Philadelphia II 4/19/40	5	P-V	8th	Frozen	Undil.	2	SC				3	2
Homewood 11/29/40	9	S-H	11th	Dried	Reconstituted to orig. volume	0.4 aa 0.2	ID			3	6	
St. Vincent's Hospital 6/17/41												
St. Mary's I A	8	PB-2	10th	Frozen	Undil.	1	IN	2	2	1	3	
B	7	PB-2	26th	Frozen	Undil.	1	IN		1		6	
C	8	PB-4	7th	Frozen	Undil.	1	IN	1	1		6	
St. Vincent's Hospital 10/22/41												
St. Raphael's I	22	PB-4	30th	Frozen	Undil.	1	INH	1	6	15		
St. Michael's I	21	PB-4	30th	Frozen	Undil.	1	ID	7	8	6		
St. Gabriel's I West	16	PB-4	35 and 36th	Frozen	Undil.	1	INH	4	4	7	1	
11/10/41 East A	10	PB-4	35 and 36th	Frozen	Undil.	0.5	ID		1	8	1	
East B	11	PB-4	35 and 36th	Frozen	1:1,000	0.5	ID		1	10		
St. Vincent's Hospital 1/8/42												
4th Floor Main I												
St. de Paul	9	PB-4	40th	Frozen	Undil.	0.5	ID	2	4	3		
Blessed Catherine	13	PB-4	40th	Frozen	1:100	0.5	ID	4	7	1	1	
St. Louise	9	PB-4	40th	Frozen	1:10,000	0.5	ID		2	7		
St. Vincent's Hospital 4/15/42					1:1,000							
St. Raphael's II	7	PB-4	66th	Frozen	Reconstituted	0.5	ID		2		5	
St. Michael's II	14	PB-4	54th	Dried	to orig. volume	0.25	ID	1	5		8	
St. Vincent's Hospital 5/11/42					Reconstituted to original							
St. Gabriel's East & West II	8	PB-4	52nd	Dried	volume	0.2	ID	1	1	5		1
Total	184							25	45	67	41	6

IN: Intranasal drip. INH: Inhalation. SC: Subcutaneous. ID: Intradermal.

severity of the reaction to virus inoculum, since frequently children with the more florid rashes would have no malaise and little or no fever. Rectal temperature elevations appeared to be the best criteria for the severity of reaction, but in this respect also there was little resemblance to the usual picture of measles, since they were short-lived, usually one to two days' elevation, and were accompanied by little or no malaise. An examining physician, conversant with typical measles, obtained an odd impression upon watching these large groups of children running about actively and happily occupied, despite the presence of numbers of Koplik spots on their buccal mucosae or well-marked and typical rashes on their skins. The nasopharyngitis and conjunctivitis were rarely obvious except in those children with moderate reactions but were readily detectable on careful physical examination.

Table II, which shows the results of inoculation of the same egg-passage virus in seventy-one children whose medical histories depended upon parents, includes twenty-eight previously mentioned, who were older children in institutions. It is evident from a comparison of this group of twenty-eight with the remaining group in the same table that the greater number of positive reactions in the later groups must have been due either to more accurate histories and thus a larger group of susceptibles or to more satisfactory egg-passage material. Though all but twelve children of the later groups were injected intradermally while the first group of twenty-eight children were injected intranasally or subcutaneously or by both routes, nevertheless, eleven of these twelve children reacted positively to their intranasal injection. These observations, therefore, appear to diminish the significance of the route of inoculation and to emphasize the importance of the negative history of measles and of the material injected. In addition, in Table I, containing those children with reliable histories, the importance of the material is again emphasized since a number of the earlier children injected showed no reactions, while in the later children practically all showed reactions, regardless of the route of inoculation.

The average length of the incubation period following inoculation of the egg-passage virus until the appearance of Koplik spots or other early signs of reaction seemed to be somewhat less than that of typical measles, since there were many children in whom the Koplik spots appeared from six to seven days from the date of inoculation. This varied from one group to another and in certain groups the incubation period was longer than that of typical measles. Several factors may have been responsible for these differences, such as the strain of virus, the number of passages, differences in the hosts, and rate of infection, etc., but with the data now available, it is impossible to determine the significance of any one of them.

Table III shows the results of exposure of susceptible controls to the children inoculated with the egg-passage virus. Unfortunately, the requirements of communal living among the groups of children studied and the apparently rapid distribution of the virus through air or by

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TABLE II

RESULTS OF INOCULATION OF ACTIVE EGG-PASSAGE MEASLES VIRUS IN CHILDREN WHOSE MEDICAL HISTORIES DEPENDED UPON PARENTS (INCLUDING 28 CHILDREN PREVIOUSLY REPORTED)

INSTITUTION, GROUP, DATE OF INOCULATION	NUMBER INOCULATED	VIRUS INOCULUM						CLASSIFICATION OF RESPONSE				
		STRAIN	PASSAGE	FROZEN OR DRIED	DILUTION	AMOUNT (C.C.)	ROUTE	MODERATE	MILD	MINIMAL	DOUBTFUL	NO POSITIVE EVIDENCE
Skillman I 1/20/39 2/16/39	4	M5 M60 Phila.	16th 11th 6th	Frozen		2	IN				3	1
Mt. Holly I 7/17/39	5	Neff	3rd, 4th, 5th pooled	Frozen		1.25	IN			1	1	3
Mt. Holly II 8/3/39	5	Cassatt	7th and 8th pooled	Frozen		1 to 2	IN				1	4
Woodbine I 10/6/39	6	Ward	20th	Frozen		2	IN					6
Woodbine II 11/2/39	8	Ward	2 {33rd, 30th} 6 {31st, 32nd}	Frozen		2	2 SC 2 SC+ IN 4 IN					8
Homewood 11/29/40	1	SH	11th	Dried	Reconstituted to original volume	0.4	ID					1
New Lisbon 3/3/41	6	Pb-2	10th	Frozen		2	IN		2	3		1

Skillman II 3/25/41	3	Pb-2	10th	Frozen		1	ID			1	1	1
Skillman III 9/17/41	4	Pb-4	22nd and 35th pooled	Frozen		1.5 to 2	INH	2		2		
St. Vincent's St. Gabriel's West 11/10/41	2	Pb-4	35th and 36th pooled	Frozen		1	IN		1	1		
Pennhurst I 11/10/41	5	Pb-4	35th and 36th pooled	Frozen		0.5	ID			5		
Pennhurst II 12/17/41	6	Pb-4	40th	Frozen	3-1:10 3-1:1000	0.5	ID			6		
St. Vincent's St. de Paul's I 1/8/42	3	Pb-4	40th	Frozen		0.5	ID	1	2			
St. Vincent's St. Louise I 1/8/42	4	Pb-4	40th	Frozen	1:10,000	0.5	ID			2	2	
Pennhurst III 3/4/42	4	Pb-4	52nd and 55th pooled	Dried	Reconstituted to original volume	0.5	ID	1	1	2		
St. Vincent's St. Raphael's II 4/15/42	1	Pb-4	66th	Frozen	1:1,000	0.5	ID			1		
St. Vincent's St. Gabriel East and West II 5/11/42	4	Pb-4	52nd	Dried	Reconstituted to original volume	0.2	ID		2	1	1	
Totals	71							4	8	25	9	25

TABLE III

RESULTS OF EXPOSURES OF SUPPOSEDLY SUSCEPTIBLE CONTROLS TO INOCULATED CHILDREN

INSTITUTION, DATE OF INOCULATION OF CONTACTS, GROUP	NUMBER INOCULATED	TYPE OF MEASLES VIRUS MATERIAL USED FOR INOCULATION OF CONTACTS				NUMBER DAYS FROM DATE OF INOCULATION OF CHILDREN TO DATE OF DISEASE IN CONTACT CONTROLS	CLASSIFICATION OF RESPONSE					MARGINAL COMMENTS
		STRAIN AND PASSAGE	FROZEN OR DRIED	DILUTION	ROUTE		MODERATE	MILD	MINIMAL	DOUBTFUL	NO EVIDENCE	
Skillman II 3/25/41 R D	1	Pb-4 10th	Frozen	Undiluted	ID	Followed for 25 days					1	P. H.*
St. Vincent's Hospital 6/11/41 St. Mary's I D	6	Pb-2 10th Pb-2 26th Pb-4 7th	Frozen	Undiluted	IN	Followed for 25 days					6	D. H.†
St. Vincent's Hospital 11/10/41 St. Gabriel's West I	3	Pb-4 35th and 36th	Frozen	Undiluted	INH	6 to 10 days[a]		1	1	1		D. H.
St. Vincent's Hospital 1/8/42 4th Main St. De Paul I	4	Pb-4 40th	Frozen	Undiluted	ID	2 in 15 days‡ 1 in 17 days 1 in 29 days	1		3[b]			D. H.
St. Vincent's Hospital 1/8/42 4th Main Blessed Catherine I	2	Pb-4 40th	Frozen	1:100	ID	1 in 23 days 1 in 25 days	1		1			D. H.
St. Vincent's Hospital 1/8/42 4th Main St. Louise I	5	Pb-4 40th	Frozen	1:10,000	ID	1 in 16 days‡ 1 in 19 days 2 in 29 days			3	1[b]	1[c]	3—D. H. 2—P. H.
St. Vincent's Hospital 4/15/42 St. Michael's II	4	Pb-4 54th	Dried	Reconstituted	ID	2 in 27 days 1 in 31 days	1			2	1	D. H.
St. Vincent's Hospital 4/15/42 St. Raphael's II	5	Pb-4 66th	Frozen	1:1,000	ID	Followed for 33 days					5[d]	D. H.
St. Vincent's Hospital 5/11/42 St. Gabriel's East and West II	7	Pb-4 52nd	Dried	Reconstituted	ID	1 in 21 days 1 in 22 days 3 in 30 days		1	2	2	2	4, D. H. 3, P. H.
Totals	37						3	2	10	6	16	

*P. H.: Data concerning child's previous negative measles history obtained from parents.

†D. H.: Data concerning child's previous negative measles history obtained from doctor.

‡These controls were intimately exposed to inoculated children in groups who showed evidence of disease on sixth to seventh days.

[a](See p. 13).

[b]One had measles in Dec., 1940.

[c]Inoc. 6/17/41 in St. Mary's Group.

[d]Two only 2 months of age.

contact at the time of inoculation, when the atomizer was used, resulted unexpectedly in an exposure of a number of the controls which coincided with the exposure of the inoculated group. If the sixteen children who showed no positive evidence and the six who showed doubtful evidence of reaction are omitted, of the fifteen remaining children two had approximately the same incubation period as the inoculated children, while thirteen had the incubation period to be expected for true contact controls, which started at the time the inoculated children showed their first signs of reaction. This small group of true contact controls is of particular interest in that the mild reaction or attenuated virus disease which the controls contracted from the inoculated children differed in no respect from that disease seen in the inoculated children. The measles virus, therefore, which had apparently been attenuated by egg passages, did not regain its normal virulence and activity by its first passage again through a human host. Whether or not successive human passages would result in a return of virulence or activity for human beings is yet to be determined.

It will also be noted from Table III that, with the exception of seven children who were exposed as contact controls in the spring and early summer of 1941, all of the other thirty contact controls were exposed to children who had been inoculated with virus of later passages; i.e., thirty-fifth to sixty-sixth. It is thus as yet unknown whether or not measles virus from the earliest egg-passages would have regained its normal virulence by a single human passage. Even among the seven children mentioned, the earliest egg passage of the virus to which they were exposed was the seventh.

The virus inoculum for most of the children was kept frozen at around –35° C. until just before inoculation. In forty children the material used was desiccated from the frozen state and reconstituted to its original volume just previous to inoculation. The distribution of reactions according to the classification of reactions outlined above was similar to the distribution noted in those children for whom the material was frozen and thawed. It may be concluded, therefore, that desiccation of the egg-passage material from the frozen state did not alter appreciably the activity of the measles virus.

The number of passages of the measles virus on the chorioallantois of the chick embryo did not appear to influence its activity after the first few passages, since material from the fifty-second and fifty-fifth passages of strain PB-4 appeared to cause as definite reactions as the virus from the earlier passages. Although only eight inoculations were carried out with the sixty-sixth passage of strain PB-4, they resulted in two mild reactions, one minimal reaction, and five doubtful reactions. In one child (E. S. in Table I) in whom virus of the fourth passage was used, a moderate reaction occurred with considerable bronchitis, which led to the use of later passage virus in other children. This result, although complicated by other factors, suggested at first that the

measles virus retained much of its normal virulence during the earlier passages, but many later inoculations revealed that further studies must be carried out with virus of early passages before this can be determined.

The strain of virus appeared to have considerable significance in relation to the consistency of the reactions produced. Strain PB-4, used for all recent studies, has appeared to be the most satisfactory in this respect. Additional studies are required to determine the importance of this factor.

Groups of children were injected intradermally with varying dilutions of the original PB-4 virus material; three children with 1:10, thirteen with 1:100, twenty-two with 1:1,000, and thirteen with 1:10,000. Although these groups were not sufficiently large for proper comparison, the reactions as indicated in Tables I and II are quite similar in all four groups, thus indicating that dilution of the material, at least up to 1:10,000, had no noticeable effect on the reactions.

Inhalation of the egg-passage virus, as described, by means of atomizing the virus material into a cellophane shower cap enclosing the child's head, resulted in reactions similar in all respects to those obtained by the intradermal method of inoculation.

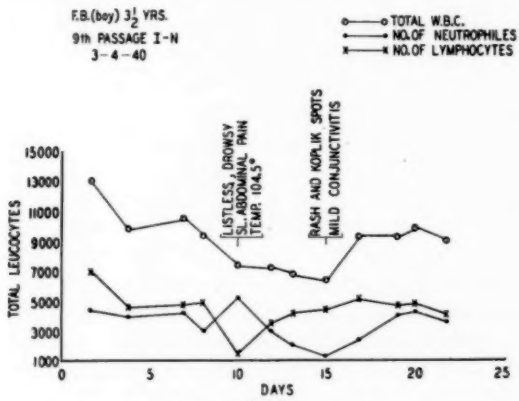

Fig. 4.

The colored illustrations, Plates I and II, show a few of the different types of rash observed, including also the rash seen in the mild simian disease. The Koplik spots as shown in these plates differ in location, size, and number in a manner similar to typical measles.

The frequent leucopenia and relative lymphocytosis accompanying the reaction to egg-passage measles virus injected into child F. B. are shown in Fig. 4.

DISCUSSION

In extension of the results obtained previously in forty children following the inoculation with egg-passage virus, typical mild measles was produced by this means in the large majority of 215 children. The

children in the later experiments were particularly important because of their preschool age range and reliable physician's history of absence of measles. The value of such selection in these groups was evident in the appearance of mild measles in approximately 74 per cent of those with a negative history from physicians. The opportunity was thereby afforded of obtaining a clearer picture of the type of disease produced by the egg-passage virus, since large groups of susceptible children could be studied simultaneously while they were showing reactions. In the majority of children inoculated with virus propagated in the egg for from twenty-six to forty serial passages, there appeared to be little difference, from one group of children to another, in the mild type of measles produced. This mild type of measles could be definitely distinguished only by the presence of Koplik spots which were typical and unmistakable in the majority of cases. The rash was often evanescent and in some children extremely sparse and, without the presence of Koplik spots, could have been readily confused with the rashes of rubella or roseola infantum (exanthem subitum) or even at times, mild miliaria. It was rarely present on the arms and legs and usually first appeared on the lower part of the face, about the ears and neck, and on the upper part of the chest. In those children with more elevated temperatures, the rash usually spread over the entire chest and abdomen, but it was very rarely of sufficient intensity to be visible at a distance from the child unless he was placed advantageously in strong daylight. The other positive signs, such as fever, coryza, and conjunctivitis, could not have distinguished the condition from any other mild upper respiratory infection. However, when combined with the Koplik spots and when seen in a large group of children simultaneously, all of whom had been inoculated at the same time with the egg-passage virus, there could be no doubt of the diagnosis of measles.

A feature which distinguished this type of measles, however, from full-blown measles or even from measles attenuated by means of human immune bodies, was the absence of cough. With the exception of a few children, little coughing was noted, even in those who suffered marked elevation of temperature. Another feature, although not so striking, perhaps, as the absence of cough, was the absence of malaise. Except for a few children, there appeared to be no decrease of general activity or playfulness, even at the height of the temperature elevation, which was usually short-lived.

From these results in the susceptible children, it appears that repeated passage on the chorioallantois of the developing chick embryo attenuates the virus of measles in a manner as yet unexplained but similar to that seen with some other viruses. A few children were inoculated with virus from early third to eleventh egg-passages, but when a comparison is made of the incidence of "moderate" reactions between those children inoculated with earlier egg-passage virus and those children inoculated with later egg-passage virus, up to the sixty-sixth passage, no significant difference is noted. Simian measles, as reported pre-

viously, is usually so mild, even following direct inoculation of body fluids from children with active measles, that contrasts in the severity of the disease are difficult to distinguish. For this reason it has been impossible thus far to utilize animal inoculation as a means of determining the degree of attenuation of the egg-passage measles virus.

From observation of the reactions produced in the contact controls, it may be said also that in the single human-to-human passages observed, the reaction was entirely similar to the reactions caused by the original egg-passage virus. There is at present no evidence to show that the attenuated virus regains its virulence by such human passage, but a greater number of passages through the human host would be necessary for the final determination of this question.

SUMMARY AND CONCLUSIONS

1. Measles virus, grown on the chorioallantois of the developing chick embryo for from three to sixty-six serial passages, was inoculated by intranasal drip, by inhalation, intradermal injection, and subcutaneous injection into 255 children, most of whom were susceptible.

2. Typical reactions of extremely mild measles occurred in the large majority of inoculated children with Koplik spots, rash, fever, conjunctivitis, and coryza but rarely with cough or malaise. In view of the nature of the reactions, the measles virus as inoculated was considered to be modified and to produce in the children an attenuated disease.

3. The passage of the attenuated measles virus again through human beings, from evidence obtained by single human passages through several "contact control" children, showed that this virus did not regain its virulence by such human passage.

4. The reactions to the inoculations emphasized the importance of the accurate negative history of measles. Significant differences in the reactions to inoculation did not appear following the use of (a) different routes of inoculation, (b) two different methods for preserving the virus material, and (c) different dilutions of the inoculum.

Our thanks are due to all who have made these studies possible, particularly to Commissioner William J. Ellis and to Dr. Ellen C. Potter of the Department of Institutions and Agencies of the State of New Jersey; to Dr. Albert W. Pigott, Superintendent at Skillman; to Miss Ruth Jones, Superintendent at Mount Holly; to Mr. E. L. Johnstone, Superintendent at Woodbine; to Miss Marie S. Winokur, Superintendent of the Homewood School; to Drs. C. T. Jones and James Q. Atkinson, of New Lisbon; to Sister Mary Clare, Superintendent, and to Dr. Morris H. Schaeffer, physician, of St. Vincent's Hospital; to Mr. E. Arthur Sweeny, Secretary of Welfare, State of Pennsylvania, and to Dr. James Dean, Superintendent at Pennhurst School. Also we wish to acknowledge the technical assistance of Mr. William P. Jambor in the preparation of the virus and the assistance of Dr. Samuel X. Radbill in obtaining fresh clinical material.

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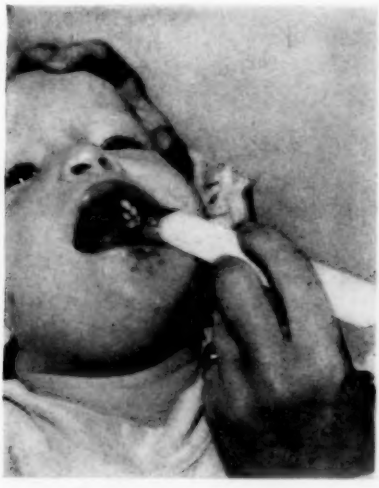
Challenge control. C. P., 10 months. Unmodified measles. Pooled blood from 4 acute measles cases. SC.

E. A. I., 11 months. "Mild." 30th passage—INH. Rash on 13th day. Highest temperature 100.8°.

A. E., 3 years. "Minimal." 35th and 36th passages pooled. ID. Rash on 22nd day. Highest temperature 100.2°.



J. T., 3 years. "Minimal." 35th and 36th passages. ID (Diluted 1:1,000). Koplik spots and rash on 20th day. Highest temperature 100.2°.

F. F., 15 months. "Moderate." 30th passage—ID. Rash on 4th day. Highest temperature 104.4°.

R. C., 13 months. "Minimal." 30th passage—INH. Rash on 13th day. Highest temperature 100.8°.

Measles in monkey following inoculation of 4th egg-passage measles virus.

Measles in monkey following inoculation of infected human blood.

STUDIES ON MEASLES

V. The Results of Chance and Planned Exposure to Unmodified Measles Virus in Children Previously Inoculated With Egg-Passage Measles Virus

Elizabeth P. Maris, M.D., Geoffrey Rake, M.B., B.S., Joseph Stokes, Jr., M.D., Morris F. Shaffer, D.Ph., and Gerald C. O'Neil, M.D.

INTRODUCTION

PREVIOUS reports[1, 2] described the production of a markedly attenuated type of measles in susceptible children inoculated with active measles virus cultivated upon the chorioallantois of the developing chick embryo. The present report is concerned with the results of exposure to measles of such inoculated children by two methods:

1. The chance exposure resulting from a school or neighborhood epidemic of measles.

2. The challenge inoculation by means of injections of blood or intranasal inoculation of nasopharyngeal secretions from children with active cases of measles during the early stages of their disease.

Exposure by both methods was necessary not only for the purpose of determining the presence or absence of immunity to measles under ordinary field conditions, but also to determine immunity under the more severe test of inoculation of active unmodified virus. Up to the present time, no satisfactory serologic test has been developed for the determination of immunity or susceptibility to measles, and the neutralization test has been possible only by the use of the relatively scarce and costly *Macaca mulatta*, or passive protection afforded to susceptible children by administering the serum of measles convalescents, a procedure which is seldom practicable for experimental studies.

METHODS

1. *Chance Exposure.*—Although it has been difficult, during these early experiments, to obtain permission from parents and guardians to inoculate children with active egg-passage measles virus, such difficulties have been slight in comparison with those encountered in persuading them to permit later direct exposure of their children to injections of blood from children with active cases of measles. For this reason, the determination of immunity in the majority of inoculated children necessarily has depended upon chance exposure. In addition, a majority of the studies concerning the results of inoculation with egg-passage

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measles virus have been conducted in institutions highly trained in the prevention of the entrance and epidemic spread of measles among their children. Thus, despite the large epidemic of measles which was prevalent in Philadelphia and the vicinity during the early months of 1941, only one of the institutions in which the inoculation studies were conducted was affected. However, fortunately for the study, one of the institutions, Homewood, sent a group of its inoculated children to a public school in which measles became epidemic early in 1941, with the result later described.

2. *Challenge Inoculation.*—The method of challenge inoculation by means of blood from children with active cases of measles has assumed increasing importance in the determination of immunity in the previously inoculated children, since it is possible by this method to obtain not only one or two controls of susceptible monkeys, but also controls of susceptible children, all inoculated with portions of the same blood or group of bloods at approximately the same time. In this method also it has been difficult to obtain controls of susceptible children. The opportunity of obtaining them has been due in great part to the assistance of the Department for the Prevention of Disease of the Children's Hospital, where the children were followed closely from birth. Their families, in matters of health, depended for advice upon this department. In presenting the reasons for such inoculations to parents of susceptible controls, it was explained that under ordinary conditions practically all individuals contract measles at some time during their lives, and that the opportunity of contracting the disease when they are in excellent physical condition, free from complicating infection and under careful nursing and isolation technique, is rarely afforded. The faith of the parents in such a rationale has been justified by the results so far obtained in controls. Their experience does not differ from that of intelligent parents who, under the supervision of the family physician, have exposed their susceptible children when they are in good physical condition in the late spring or early summer, to cases of measles. Up to the present time this method of producing immunity to measles, although obviously difficult to carry out for many reasons, nevertheless has had satisfactory results. This method has appeared to be safer in recent years with the advent of the sulfonamide drugs for the control of complicating bacterial infections. Two of the control children were isolated in cubicles supplied by air from out-of-doors which was suitably heated and humidified, while the others were isolated with nurses in a special isolation ward of the Children's Hospital. The material for injection of the monkeys, of the children to be challenged, and of the control children, with the exception of one instance in which nasopharyngeal secretions were used, has all been defibrinated blood from several children with active measles stored at low temperature for varying short periods of time and finally pooled in a single batch. The inoculations of blood in the children were all in-

tramuscular into the buttocks, except the Mt. Holly groups, which were injected subcutaneously.

RESULTS

Chance Exposure.—The children in this category were all exposed during the epidemic of measles occurring early in 1941 and may be divided into four groups:

1. One child, E. S., female, aged 5 years, in a physician's family, was inoculated on Jan. 3, 1940, intranasally and subcutaneously with 2 c.c. of fourth egg-passage measles virus by each route and showed a moderate* reaction with typical Koplik spots, a moderate amount of fever, cough, and a few questionable macules. Approximately one year later, in 1941, she was exposed by chance to measles in her schoolroom and did not contract the disease.

2. This group included five children who had been followed from birth in the nutrition clinic of the Children's Hospital and who were exposed to cases of measles in their neighborhood.

(a) L. P., male, aged 4 years, was inoculated by the intranasal drip method with 2 c.c. of ninth egg-passage measles virus material on March 4, 1940, but failed to show any typical signs of measles at this time. On April 17, 1941, following a neighborhood exposure, he suffered an attack of very mild measles which cleared completely within thirty-six hours (see Table I).

(b) Frances B., female, aged 5 years, was inoculated by the intranasal drip method with 2 c.c. of ninth egg-passage measles virus material on March 4, 1940, and showed a minimal measles reaction with questionable Koplik spots and no fever or rash for two days, starting on March 7, 1940. On Feb. 9, 1941, following a neighborhood exposure, she suffered a moderately severe case of measles with the highest temperature reaching 102.5° F. Following a normal temperature for three days, it again rose to 103° F. on Feb. 15, 1941, and she suffered a questionable bronchopneumonia which subsided rapidly following the use of a sulfonamide preparation (see Table I).

(c) Frank B., male, 3 years (brother of Frances B.), was inoculated on the same day and by the same method, amount, and type of material as his sister and showed a moderate reaction beginning on March 13, 1940, with a temperature of 104.5° F., a slight conjunctivitis, and slight abdominal pain. These symptoms and signs disappeared for five days, following which he had a few Koplik spots and definite slight but morbilliform rash without fever. About one year later he was exposed to his sister throughout her attack of moderately severe measles, beginning on Feb. 9, 1941. On Feb. 21, 1941 his temperature rose to 100.2° F., with a few Koplik spots, a slight cough, and a very light rash. His

*For classification of reactions of children to egg-passage measles virus, see Study IV, p. 1, of this issue.

TABLE I

RESULTS OF EXPOSURE OF INOCULATED CHILDREN TO MEASLES PREVALENT IN THE COMMUNITY

GROUP, NUMBER OF INDIVIDUALS, DATE VACCINATED	PARENTAL OR DOCTOR'S HISTORY	MEASLES VIRUS MATERIAL USED FOR INOCULATION	ROUTE	AMOUNT (C.C.)	APPARENT REACTION* TO VACCINATION	TYPE OF EXPOSURE TO NATURAL DISEASE	DATES OF EXPOSURE	TIME INTERVAL FROM INOCULATION TO EXPOSURE	CLASSIFICATION OF RESPONSE TO EXPOSURE TO MEASLES	REMARKS
Philadelphia 1 (E. S.) 1/30/40	D	H-D (4th passage)	IN+ SC	2 each route	Moderate	Casual, school-room	Winter, 1941	Approx. 1 year	No disease	Usual severity in school cases
Philadelphia I 3 3/4/40	D	PV (9th passage)	IN	1 to 2	1 moderate 1 minimal 1 no evidence	1 intimate, home; 1 school 1 community	Winter, 1941	Approx. 1 year	1 very mild 1 typical course 1 modified	Typical disease of usual severity in contacts
Philadelphia II 2 4/19/40	D	PV (8th passage)	SC	2	2 doubtful	1 casual, community; 1 intimate, home	Winter, 1941	Approx. 1 year	1 extremely mild 1 no disease	Contacts had typically severe disease, as far as could be determined
Homewood 10 11/29/40	9 D 1 P	SH (11th passage)	ID	0.4	3 minimal 6 doubtful 1 no evidence	7 intimate, school; 3 institution; probably casual	2-mo. period Winter, 1941	3 to 5 months	10 no disease	25 out of 36 susceptible children in school contracted measles of usual severity
New Lisbon 6 3/3/41	P	Pb-2 (10th passage)	IN	2	2 mild 3 minimal 1 no evidence	Very intimate, dormitory	June-July, 1941	2 to 4 months	2 typical severe measles 1 extremely mild 3 no disease	Disease severe—approximately 60 cases in colony; between 20 and 30 in dormitory where 4 previously inoculated were constantly exposed

*See Study IV, p. 1, of this issue.
IN: Intranasal drip.
SC: Subcutaneous.
ID: Intradermal.

fever subsided within a few hours and he had no malaise, his mother describing his case as "a real pleasure" (see Table I).

(d) S. G., male, 3 years, was inoculated subcutaneously with 2 c.c. of eighth egg-passage virus material on April 19, 1940, and showed a doubtful reaction, without rash or Koplik spots, on May 1, 1940. He had a marked adenitis, pharyngitis, and temperature of 104.5° F., signs which were probably due to an intercurrent infection. In March, 1941, following a neighborhood exposure to measles, he had one day of mild fever, slight cough, and rash, without malaise. Notification was not sufficiently early to permit examination for Koplik spots, but the rash, though slight, was typical, and measles was widely prevalent in the neighborhood. He was not put to bed at any time, since he had no malaise and was lively and happy.

(e) E. G., male 2 years, was inoculated in a similar manner to his brother, S. G. He suffered respiratory infection similar to his brother's but milder in character, which did not resemble measles. In contrast to his brother, he had a slight erythematous punctate rash on the twelfth day which faded in a few hours. He was exposed to his brother, S. G., in March, 1941, and was examined daily for eighteen days following S. G.'s attack. He showed no evidence of measles at any time.

3. The third group included six children who were exposed by chance to an epidemic of measles in the younger boys' cottages in the New Lisbon State Colony New Jersey (see Table I). The original inoculation of this group on March 3, 1941, was described in the previous report[1] (see Table II of Study IV) and was carried out by the intranasal drip method with tenth egg-passage virus material.

(a) E. A., male, 16 years, showed a minimal reaction to the egg-passage virus. He experienced repeated and intimate exposure to many cases of severe measles in a closely packed dormitory from June 5, 1941, to July 20, 1941, which was a little over three months from the time of his inoculation with egg-passage material, but remained free from measles.

(b) G. D., male, 16 years, showed a minimal reaction to egg-passage virus. After exposures similar to those of E. A., he had bouts of a transient erythematous blush with no fever or malaise from June 5, 1941, to July 20, 1941 but without anything characteristic of measles. He had been subject to skin reactions of this type previously, and they were probably of little significance.

(c) W. L., male, 14 years, showed a mild reaction to egg-passage virus. Blood obtained from this boy at the height of his inoculation reaction caused typical simian measles in a *Macaca mulatta*. After exposure to many cases of measles on June 5, 1941, and subsequently, he suffered severe typical measles with severe blepharitis and high fever, beginning on June 20, 1941.

(d) R. L., male, 14 years, showed a minimal reaction to egg-passage virus. After exposure similar to the above, he showed on July 12, 1941,

a temperature of 99.4° F. and Koplik spots without cough, rash, malaise, or conjunctivitis. He was not put to bed and had not frequent examinations been made, nothing would have been suspected in his case. His temperature elevation lasted only a few hours, and since it was midsummer and extremely warm weather, it may have had no significance.

(e) J. N., male, 15 years, showed a mild reaction to egg-passage virus. Blood obtained at the height of his inoculation reaction produced typical simian measles in the *Macaca mulatta*. After exposures to natural measles similar to the above, he developed no signs or symptoms of any type.

(f) R. S., male, 14 years, showed no evidence of reaction to egg-passage virus. After exposures similar to the above, he developed moderate uncomplicated measles on June 7, 1941, three months following inoculation. It may be significant that he alone of the six boys showed no reaction at the time of his inoculation.

4. In the fourth group (see Table I), which included 10 children followed from birth in the Homewood Orphanage, Germantown, Pa., the children were inoculated on Nov. 29, 1940, with 0.2 c.c. of eleventh egg-passage virus material intradermally in each forearm and showed insignificant reactions (see Table II of Study IV). The three youngest of this group were exposed by chance to two cases of measles occurring in the Infant Dormitory but did not develop measles. The remaining seven were exposed by chance to an epidemic of measles occurring in the Keyser Public School, which was attended by most of the children of the orphanage. A severe epidemic of measles swept through this public school from February to June of 1941, but despite the fact that the seven children were all intimately exposed to many cases in five different classes, none of them contracted measles.

TABLE II

RESULTS OF EXPOSURE OF SUSCEPTIBLE CHILDREN IN KEYSER PUBLIC SCHOOL (WINTER, 1941)

SCHOOL CLASSROOM	NONINOCULATED (36)		INOCULATED (7)	
	MEASLES	NO MEASLES	MEASLES	NO MEASLES
Kindergarten Group A	2	4	0	2
Kindergarten Group B	8	4	0	2
Kindergarten and First Grade A Combined	4	1	0	0
First Grade B	6	2	0	1
Second Grade A	5	0	0	2
Totals	25	11	0	7

The results of this chance exposure are best shown in Table II which compares the incidence in the susceptible children who had not been inoculated with the small group of inoculated children. It will be noted that twenty-five of the thirty-six noninoculated susceptible children contracted measles, whereas none of the seven inoculated children contracted the disease. Although statistical analysis may not afford

conclusive findings when such small groups are involved, nevertheless, the results of applying the X_2 test to these data appear highly favorable to the protective value of the inoculation. In addition, the unusually high incidence of measles in the rest of the children in the classes suggested a very intimate exposure to the disease.

Challenge Inoculation.—The children in this category may be divided into three groups (see Table III).

1. There were thirteen children in the first group, which includes all of those children previously tabulated.[1] These children were resident in Skillman, Mt. Holly, and Philadelphia, only the last group having been followed from birth. In summary, two children from Skillman were challenged with nasopharyngeal washings from patients with active cases of measles four weeks following their second inoculation with egg-passage virus by the intranasal drip method. Neither of these children contracted measles. A third child at Skillman was challenged similarly, four months following his original inoculation with egg-passage virus and showed no measles. A monkey injected with a portion of the challenge material used for the first two children contracted simian measles, whereas the monkey injected with challenge material for the third child died of previously existing tuberculosis before any obvious reaction to the measles virus could be expected. The five children from Mt. Holly were challenged with pooled blood from patients with active cases of measles approximately nine months following their inoculation by intranasal drip with egg-passage virus. None of these children showed any reaction to the challenge injection, whereas the two control children and the control monkey injected with portions of the same blood all developed measles which was typical for the species injected (see colored illustrations, Plates I and II.)

Two of the children of Philadelphia Group I were challenged with pooled blood of patients with active measles five weeks following inoculation of egg-passage measles virus by intranasal drip, to which one had shown a doubtful reaction and the other no evidence of reaction. Both children showed typical modified measles similar to that produced by human immune bodies when used in passive immunization. One monkey control for these two children developed typical simian measles. Three of the children of Philadelphia Group II were challenged similarly two months following subcutaneous injection of virus material which was considered to be inactive and to which they had shown very doubtful or no evidence of reaction. All three children developed frank, unmodified measles. Two monkey controls for these three children also developed typical simian measles. This same egg-passage material, injected subcutaneously, in two other Philadelphia children, siblings, at the same time may have partially protected these children against measles (see Table I, E. G., and S. G.). The difference between the responses of these two groups may have been due either to the greater

TABLE III

SUMMARY OF CHALLENGE INOCULATION OF PREVIOUSLY VACCINATED CHILDREN

GROUP, DATE OF CHALLENGE, AND NUMBER OF CHILDREN	PARENT'S OR DOCTOR'S HISTORY	MEASLES VIRUS USED FOR ATTEMPTED IMMUNIZATION	AMOUNT (C.C.) AND ROUTE	APPARENT REACTION TO VACCINATION	MEASLES VIRUS USED FOR CHALLENGE INOCULATION	AMOUNT (C.C.) AND ROUTE	TIME INTERVAL BETWEEN VACCINATION AND CHALLENGE	DEGREE OF RESPONSE TO CHALLENGE	REMARKS
Skillman I 4/19/40 3	P	1/20/39 to 2/16/39 Pb-6 (6th passage) M-60 (11th passage) V-5 (16th passage)	2, IN	2 doubtful 1 no evidence	Nasopharyngeal washings from acute measles case (W.) to 2; nasopharyngeal, washings from acute measles case (E.) to 1	2, IN	3 to 4 months	3 no disease	(W) material given to Macaca mulatta 71 produced simian measles, 14th to 18th day (E) material to Macaca mulatta 68—died on 8th day of tuberculosis
Mt. Holly I 3 Mt. Holly II 2 3/25/42	P	7/17/39—Neff 2nd, 4th, and 5th passages 8/3/39—Cassatt 7th and 8th passages	1 to 2 IN	1 minimal 1 doubtful 3 no evidence	Pooled blood from 4 fresh cases of measles kept between 4 hr., and 9 days before pooling and use for inoculation	2.5, SC	7½ to 8 months	5 no disease	2 control children, P. and M., given same challenge material contracted typical moderately severe measles
Philadelphia I 4/18/40 2	D	3/4/40 PV (9th passage)	1 to 2 IN	1 doubtful 1 no evidence	Pooled blood from 3 fresh measles cases 2 frozen 11 days, 1 kept cold 2 days; all pooled before use	2.5, IM	5 weeks	1 slightly modified measles 1 greatly modified measles	Macaca mulatta 105 given same pooled blood, developed simian measles

Philadelphia II 6/21/40 3	D	4/19/40 PV (8th passage	2 SC	1 doubtful 2 no evidence	Pooled blood from 2 fresh measles cases (B and S) B. frozen 5 days; S. kept cold 1 day; pooled for use within 24 hours	2, IM	2 months	3 typical unmodified measles	Macaca mulatta monkeys 89 and 92, given same challenge material, contracted simian measles
Pennhurst I 3/23/42 5	P	11/10/41 Pb-4 (35th and 36th passage)	0.5 ID	5 minimal	Pooled blood from 3 fresh measles cases (G., H. and McC); frozen 14 hr. to 44 days then pooled immediately before use	1, IM	4½ months	2 extremely mild measles 3 no disease	2 children (Mi. and Ma. H.) given same pooled material on same day; both developed mild measles
Pennhurst II 4/13/42 6	P	12/17/41 Pb-4 (40th passage) 3/ 1:10 dilution 3/ 1:1,000 dilution	0.5 ID	6 minimal	a. Unpooled blood from R. L., fresh measles case (30 hr. past initial rash); kept cold, then frozen 5 days before use b. Unpooled blood from E. M., fresh measles (12 hr. after initial rash); kept cold, then frozen 5 days before use	1.5, IM. left gluteus; 1, IM right gluteus	4 months	3 extremely mild measles 1 doubtful response 2 no disease	2 children (R. M. & T. S.) given same bloods in same manner (unpooled) on same day; T. S. very mild measles R. M. S. doubtful; showed no *typical* Koplik spots

IN: Intranasal drip.
SC: Subcutaneous.
IM: Intramuscular.

severity of the test in the challenge inoculation of the group of three children or to the longer interval between inoculation and exposure of the two siblings.

2. There were 5 children in the second group, who had each been previously inoculated intradermally with 0.5 c.c. of thirty-fifth and thirty-sixth pooled egg-passage measles virus on Nov. 10, 1941, at the Pennhurst School, Pennsylvania. All showed minimal reactions (see Study IV). Four and one-half months later, each of them was challenged with 1 c.c. of pooled blood from three children with active cases of measles. Two of them, R. A. and F. N., showed minimal reactions as indicated in Table III. R. A. showed five Koplik spots on the tenth day and a temperature of 100° F. on the afternoons of the fourteenth and fifteenth days, with no rash, cough, malaise, or any other evidence of measles. F. N. showed two Koplik spots and a few light pink confluent macules on the trunk and forearms on the twelfth day, without fever or other signs, the Koplik spots disappearing after one day and the rash disappearing by the fifteenth day. The other three children showed no evidence of disease (see Table III). Later on the same day that these five children received their challenging inoculation of blood, two susceptible siblings, Ma. H., and Mi. H., followed from birth by physicians of the Children's Hospital, were each injected intramuscularly into the buttocks with a 1 c.c. portion of the same pooled blood. These siblings, Mi. H. 4½ years of age, male, and Ma. H., 2½ years of age, female, developed definite but mild measles. Mi. H. showed a typical hacking cough, a fever for four days, reaching 100.6° F. on the ninth day, a number of Koplik spots from the tenth to the fifteenth day, anorexia, irritability, malaise, diarrhea, conjunctivitis, and a light red discrete macular rash over the face, neck, and trunk, beginning on the seventh day and fading on the eighteenth day. Ma. H. showed a mucous discharge but no cough from the third to the sixteenth day, moderate irritability and anorexia from the eighth to the fourteenth day, conjunctivitis with slight photophobia from the thirteenth to the sixteenth day, a few Koplik spots on the thirteenth and fourteenth days, a light but typical morbilliform rash over the face and legs beginning on the tenth day and fading by the twentieth day, and fever over eight days with a maximum of 100.8° F.

3. There were six children in the third group who had been previously inoculated intradermally with 0.5 c.c. each of fortieth egg-passage measles virus on Dec. 17, 1941, at the Pennhurst School. The inoculum was diluted 1:10 for three of the children, M. McK., F. S., and V. S.; and 1:1,000 for the remaining three children, M. O'B., B. J. R., and G. R. All six children showed minimal reactions (see Table II, Study IV). On April 13, 1942, four months later, each of these six children was challenged with intramuscular injections of blood from two children with active cases of measles; 1.5 c.c. of blood from R. L., who had an active case of measles, was injected into the left buttock of each

of the six children and 1 c.c. of blood from E. M., who had an active case of measles, was injected into the right buttock of each child. Of those children receiving the 1:10 dilution of the original vaccine, M. McK., following the injection of blood, showed irritability on the eleventh day, Koplik spots from the twelfth to sixteenth day, a light scattered macular rash on the face, neck, and anterior trunk from the fifteenth to the nineteenth day, but no fever, conjunctivitis, or respiratory signs; F. G., following the injection of blood, showed no evidence of measles; and V. S., following the same blood, had no Koplik spots or respiratory signs of any sort but on the eleventh and twelfth days showed about fifty light pink scattered macules on her neck and trunk.

Of those children receiving the 1:1,000 dilution of the original vaccine, M. O'B., following the injection of blood, had an increase in her chronic nasal discharge from the ninth to the nineteenth day, a few Koplik spots on the twelfth day, and irritability on the fifteenth and sixteenth days without fever, cough, or other signs. B. J. R., following injection of the same blood, had no evidence of measles; and G. R., following injection of the same blood, had a few Koplik spots from the twelfth to the fifteenth day, with no cough, malaise, or any other sign or symptom of measles.

Later on the same day that these six children received their challenging inoculations of blood, two susceptible siblings, R. M. S., and T. S., followed from birth by physicians of the Children's Hospital, were each injected intramuscularly with 1 c.c. of blood from R. L., and with 1 c.c. of blood from E. M. separately into each buttock, as described above.

T. S., a male, 4 years of age, showed irritability from the tenth to the eleventh day, a mild fever reaching 100.2° F. on the tenth and eleventh days, a mild hacking cough from the ninth to the thirteenth day, a watery nasal discharge on the eleventh and twelfth days, a mild conjunctivitis with photophobia on the eleventh day, a few Koplik spots on the ninth and eleventh days, six discrete macules on the anterior chest on the ninth day, and mild malaise, irritability, and anorexia on the tenth and eleventh days. R. M. S., female, 2 years of age, was restless and irritable on the eleventh and twelfth days, had fever from the ninth to the twelfth day reaching 100.2° F., slight mucous nasal discharge on the eleventh day, hacking cough from the ninth to the eleventh day, no definite Koplik spots, but the mucosa was erythematous and blotchy on the eleventh day, with approximately a hundred typical pink macules over the chest and abdomen from the eleventh to the thirteenth day.

DISCUSSION

In reviewing the results of these studies, the important finding is the complete protection of twenty-three of the forty-six children inoculated with egg-passage virus from chance exposure to measles or chal-

lenge inoculation with body fluids from children with active cases of measles. An additional five children also remained free of the disease after challenge inoculations, but since the two control cases showed very mild measles, the degree of protection cannot be estimated for this group. Of those children who were not completely protected, there were but six who exhibited unmodified measles, and these were evenly divided between the group exposed by chance and the challenged group. When the twelve children whose disease was significantly modified are included with those who had no disease, the egg-passage measles virus appears to have completely or partially protected forty of the forty-six children inoculated. The chance exposure of seven of the children in the Keyser Public School was extremely intimate and none of these contracted measles in contrast to twenty-five cases of measles among the other thirty-six susceptible children in the same grades (see Table II). From the data at hand, it is impossible to determine the relation between the amount of reaction to the egg-passage virus and the degree of immunity produced.

Another factor, possibly modifying the degree of immunity, which it is as yet impossible to evaluate in relation to the factors already mentioned, is the effect on immunity of the length of time between the inoculation with egg-passage virus and the later exposure to the unmodified virus. Since second cases of measles, under ordinary conditions, are comparatively rare,* the unmodified measles virus must usually effect a solidly immune state in the host. Whether or not this is also true of the virus as modified by egg-passage is still obscure and must be the object of further extensive studies over a period of years.

It has not been possible as yet to determine the value of the inhalation method of inoculation with egg-passage virus, since no chance exposures have occurred in this group nor has permission been granted for challenge inoculations of these children.

It should also be pointed out that in view of the lack of satisfactory tests for susceptibility or immunity in man or monkey and in view of the fact that these studies are dealing with an agent which cannot as yet be determined by quantitative methods, progress in the field of active immunization must of necessity be slow. However, considerable advantage, in such studies, accrues from the fact that measles is an almost universal disease, and it should be possible within a few years to determine whether or not immunity can be produced by measures similar to those described. Whether or not a permanent or solid immunity can be so produced remains for an even longer period to decide.

Evidence so far available gives no indication as to the wisdom of using inocula from earlier egg-passages or as to the possibility that a mild or possibly transient immunity produced may be strengthened to a permanent or solid immunity by means of later use of unmodified

*There is some difference of opinion concerning the degree of immunity conferred by measles markedly modified by human immune bodies.

virus. The use of virus inactivated by various methods still requires study, together with the development of quantitative and qualitative methods for study of the virus.

SUMMARY

1. Twenty-two children who had been previously inoculated with egg-passage measles virus were exposed by chance at various intervals up to one year from the time of their inoculations to children with active cases of measles under field conditions. Three of these children developed typical measles, one developed mild measles, three developed an extremely mild disease distinguishable with difficulty as measles, and fifteen developed no disease.

2. Twenty-four children who had been previously inoculated with egg-passage measles virus were exposed by challenging injections of blood from active cases of measles at various intervals from the time of their original inoculations. Three of these children developed typical measles, two developed mild measles, five developed an extremely mild disease distinguishable with difficulty as measles, and thirteen developed no disease. One additional child showed a slight nasopharyngitis without fever, rash, or Koplik spots.

Suitable control children and monkeys were injected with portions of the challenge material used and developed measles typical for the species injected.

3. The use of measles virus, attenuated by passage on the chorioallantois of the developing chick embryo, for active immunization of children against measles gave results sufficiently encouraging to warrant further trial of such immunization in larger groups of susceptible children under field conditions inasmuch as forty of the forty-six children inoculated appeared to be completely or partially protected from measles.

Our thanks are due to all who have made these studies possible, particularly to Commissioner William J. Ellis and to Dr. Ellen C. Potter of the Department of Institutions and Agencies of the State of New Jersey; To Dr. Albert W. Pigott, Superintendent at Skillman; to Miss Ruth Jones, Superintendent at Mount Holly; to Mr. E. L. Johnstone, Superintendent at Woodbine; to Miss Marie S. Winokur, Superintendent of the Homewood School; to Drs. C. T. Jones and James Q. Atkinson, of New Lisbon; to Sister Mary Clare, Superintendent, and to Dr. Morris H. Schaeffer, physician, of St. Vincent's Hospital; to Mr. E. Arthur Sweeny, Secretary of Welfare, State of Pennsylvania, and to Dr. James Dean, Superintendent at Pennhurst School. Also we wish to acknowledge the technical assistance of Mr. William P. Jambor in the preparation of the virus, and the assistance of Dr. Samuel X. Radbill in obtaining fresh clinical material.

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CHRONIC HEMOLYTIC ANEMIA WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (MARCHIAFAVA-MICHELI SYNDROME)

Report of a Case With Marked Thrombocytopenia in a Five-Year-Old Child

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HEMOGLOBINURIA, in contrast to hematuria, is a clinical sign which is so seldom seen in pediatric practice that its appearance is a matter of unusual interest and significance. The occurrence of hemoglobinuria depends in all cases upon excessive destruction of erythrocytes with the liberation of hemoglobin into the circulating blood plasma in greater amounts than the phagocytes of the endothelial system can metabolize. Under normal conditions, the blood plasma contains no free hemoglobin. Although a renal threshold exists for this substance, it appears to vary in different individuals.

Causes of Hemoglobinuria.—There are numerous causes of hemoglobinuria if patients of all ages are considered, although some of them are rarely, if ever, responsible for its occurrence in children. Kracke[8] subdivides this condition into exogenous, endogenous, and paroxysmal types. Of the exogenous type, such causes as chemical agents, febrile intoxications, malaria and other parasitic diseases, transfusion of incompatible blood, severe burns, and cobra and spider venom are cited.

The endogenous type includes the various hemolytic anemias in which large numbers of erythrocytes are destroyed during severe hemolytic crises. Of these the most common are the familial and acquired forms of hemolytic icterus, acute hemolytic anemia of Lederer, erythroblastic anemia (Cooley's), and sickle cell anemia.

Paroxysmal hemoglobinurias include paroxysmal cold hemoglobinuria, paroxysmal march hemoglobinuria, and paroxysmal nocturnal hemoglobinuria.

Paroxysmal Nocturnal Hemoglobinuria (Marchiafava-Micheli Syndrome).—This rare disease was first described by Marchiafava and Nazari[11] in 1911. In 1928 and 1931 Marchiafava[9, 10] again reported on the condition as did Micheli[12] in 1931. Because of these articles, the disease is frequently referred to as the Marchiafava-Micheli syndrome. Although less than fifty cases have been reported to date, the disease is becoming better known, most of the cases having been recognized during the past decade.

Recent descriptive articles and case reports appearing in American and British journals have been written by Hamburger and Bernstein[7]

From The Children's Memorial Hospital.

(1936); Witts[15] (1936); Ham[3, 4] (1937, 1939); Dacie, Israels, and Wilkinson[2] (1938); Scott, Robb-Smith, and Scowen[14] (1938); Ham and Dingle[5] (1939); Ham and Horack[6] (1941); and Buell and Mettier[1] (1941).

Characteristics.—The outstanding clinical features of the disease are chronic hemolytic anemia which is resistant to treatment, constant hemoglobinemia, and an associated paroxysmal type of hemoglobinuria which is induced by sleep. Continuous intravascular hemolysis occurs, but the most severe degree of erythrocyte destruction occurs whenever the patient sleeps. This is not influenced by the time of day or night, by posture, or by food or fluid intake. There is no known association with the presence of any specific type of infection in the body, although in established cases, the degree of hemoglobinuria has been observed to be more severe during periods of active infection.

At intervals following severe hemolytic episodes, dark reddish brown or black urine is excreted. This gives a strongly positive reaction to the benzidine test for blood. In most specimens, no erythrocytes are found on microscopic examination, although a few shadow forms of red blood cells may occasionally be seen. Specimens which contain hemoglobin give a positive reaction for albumin. Urine which is voided during or immediately following sleep may show large amounts of hemoglobin, while the specimens which are obtained a few minutes or a few hours after the patient has awakened are frequently negative for hemoglobin or may show only a minimal amount.

Such paroxysms may persist for a few hours or for several days or weeks and then will be followed by a period of days, weeks, or months in which the urine is normal even though hemoglobinemia is always present. Hemosiderinuria is also constantly present.

The anemia may be classified as a normocytic or slightly macrocytic type. The red blood cell count usually ranges between one and three million cells per cubic millimeter and the hemoglobin, from 20 to 60 per cent. There is a constant reticulocytosis which commonly varies from 10 to 30 per cent. Moderate leucopenia and thrombocytopenia have frequently been noted. The differential leucocyte count is usually normal, but there may be a slight lymphocytosis. The erythrocytes show normal resistance to hypotonic saline solutions.

The outstanding symptoms are recurrent attacks of severe abdominal or lumbar pain which are frequently associated with chills, fever, and general malaise. Hemoglobinuria may or may not be noted following such an attack. Although a mild icteric tint of the skin and sclerae may be present all of the time, it is frequently of greater intensity following hemolytic crises. The patient usually complains of weakness which is consistent with the degree of anemia present.

In addition to the pallor and icterus, physical examination sometimes reveals a moderate degree of hepatomegaly and splenomegaly. Pathologic studies of patients who have died of the disease have shown vas-

cular thromboses, some degree of necrosis of the liver in the region around the central veins, hemosiderin deposition in the convoluted tubules of the kidneys, and hyperplastic bone marrow. No characteristic changes have been found in the spleen.

Age and Sex Incidence.—A review of the literature reveals a total of forty-seven reported cases. In none of these patients has the onset been known to occur in the preadolescent years. The youngest on record, reported by Ham,[4] was first observed at the age of 17 years with an onset apparently two years earlier. The oldest patient reported (Scott, Robb-Smith, and Scowen[14]) was 52 years old. The greatest number have been in the third and fourth decades of life. The age distribution is shown in Table I.

TABLE I

AGE IN YEARS	CASES
0 to 10	0
10 to 20	6
20 to 30	13
30 to 40	17
40 to 50	9
50 to 60	1
Age not given	1

Of the forty-seven cases, there have been twenty-three males and twenty-four females. This report, which is of a male, makes the division between the sexes equal.

Etiology.—Various theories have been proposed to explain a possible cause of this condition. One of these has been the idea that long-standing sepsis may cause the bone marrow to produce erythrocytes of poor quality, although infection has not been demonstrated in all of the patients. Another considers the possibility of an allergic reaction to foodstuffs or intestinal toxins, but this is not borne out by sensitivity tests. Any relationship of the hemoglobinuria to food or fluid intake, position of the body during sleep, or to meteorologic conditions has remained undemonstrable.

In 1939 Ham[4] reported investigations conducted on the mechanism of hemolysis in five patients with this disease. He showed that the fundamental factor in the hemolytic process lies in an abnormality of the patients' erythrocytes which makes them unusually susceptible to very slight changes toward the acid side in the pH of the blood plasma. A thermolabile factor which was indistinguishable from human complement was also found to be necessary for in vitro hemolysis. From these observations, Ham concluded that the intravascular hemolysis occurs particularly during sleep because the pH of the blood plasma is decreased a very slight but significant amount within physiologic limits due to diminished pulmonary ventilation and resultant increased carbon dioxide concentrations. He showed that hemolysis and hemoglobinuria can be increased in patients suffering from the disease by oral admin-

istration of acid salts such as ammonium chloride. By giving sodium bicarbonate orally, the hemolysis was temporarily decreased, but this was found to be inadvisable as a method of treatment because a severe exacerbation followed discontinuance of the medication.

Differential Diagnosis.—The chief diseases from which this syndrome must be distinguished are the previously mentioned forms of paroxysmal hemoglobinuria, familial hemolytic icterus, Lederer's anemia, Cooley's anemia, and sickle cell anemia.

Paroxysmal cold hemoglobinuria is a rather rare manifestation of congenital or acquired syphilis in which the hemoglobinuria always follows chilling of the entire body or a part of it. An autohemolysin is present in the blood plasma which unites with the erythrocytes at low temperatures and causes hemolysis when the temperature returns to normal. This autohemolysin is demonstrable in vitro in the Donath-Landsteiner reaction. No abnormality of the erythrocytes is present.

Paroxysmal march hemoglobinuria depends entirely upon the factor of physical exertion. It occurs chiefly in healthy young males and has been observed particularly in soldiers after long marches. There is no relation to syphilitic infection, exposure to cold, any particular type of food or drugs, or any abnormality of the red blood cells. Anemia is usually absent or, if present, is quite transient. The tendency to this reaction usually disappears without treatment and without residual complications.

Allergic hemoglobinuria has been reported as a type of reaction which occurs after the ingestion of beans from the plant *Vicia fava* or from inhalation of its pollen. This condition has been observed principally in Sicily, Sardinia, and southern Italy, where the favus beans are used as food.

Paralytic myoglobinuria has erroneously been classified with the hemoglobinurias. The dark brown urine which is voided in this condition is found to contain myoglobin rather than hemoglobin, and there is no associated lysis of erythrocytes and no anemia is present.

In familial hemolytic icterus, hemoglobinuria occurs after severe hemolytic crises, but there is no relationship to sleep. Spherocytosis is observed on microscopic examination of the blood, and there is increased fragility of the erythrocytes in hypotonic saline solution. There is no increased fragility, however, in acidified serum, as is the case in the Marchiafava-Micheli syndrome. A familial tendency is present. Splenomegaly is always present, and splenectomy is effective in the treatment of this condition.

The acute hemolytic anemia of Lederer occurs chiefly in infants and children and pursues a rapid course, but these patients usually respond to transfusion if it is started early enough. It usually does not recur.

Sickle cell anemia occurs almost exclusively in the Negro race. The finding of the characteristic sickle-shaped red blood cells in stained films

or wet preparations in a Negro with severe anemia, icterus, recurrent attacks of fever, and abdominal pain is almost pathognomonic of the disease.

Erythroblastic anemia of Cooley usually occurs in people of Mediterranean ancestry. The onset is usually in infancy or early childhood. In addition to evidence of a severe hemolytic anemia, large numbers of erythroblasts are usually found in the peripheral blood. Splenomegaly is a prominent feature, and the typical mongoloid facies is present in most cases.

Prognosis.—Many of the patients in the reported cases of paroxysmal nocturnal hemoglobinuria have died following surgical procedures which were intended to cure the disease. Of these procedures, splenectomy has been the most common. Rosenthal's[13] patient died as a result of splenectomy thirty-three years after the onset of the disease. Others have lived with only moderate disability for a number of years. Vascular thromboses in various parts of the body have been the cause of death and disability in a number of the patients.

The disease has seldom been fatal in its early stages except where surgical intervention has resulted in death. As a rule, however, it has proved fatal after a prolonged course with remissions and exacerbations.

Treatment.—Although splenectomy has been the most frequently used form of treatment, it has failed to prove effective in curing the condition and has resulted in several deaths. Ham[4] reported that one of his patients did not show hemoglobinuria after splenectomy, although the fundamental abnormality of the erythrocytes persisted and the degree of the anemia was not altered. Other operations which have been performed, principally due to mistaken diagnoses, are nephrectomy, cholecystectomy, and exploratory laparotomy.

Various forms of medical management have been employed. Transfusions in many cases have been followed by severe hemolytic reactions and exacerbation of the hemoglobinuria. Sun lamp radiation at night has been tried in an attempt to circumvent the nocturnal factor in the hemoglobinuria. General supportive measures, such as oral administration of iron, accessory food factors, a liberal diet, and the avoidance of infections, have been found to be most effective in prolonging life and improving the well-being of the patients. The administration of liver extract has been found to be ineffective in altering the course of the anemia.

CASE REPORT

K. C., a 5½-year-old white boy of Irish and Lithuanian descent, was admitted as a private patient to The Children's Memorial Hospital on Feb. 21, 1941, upon referral from a physician in a suburban town.

It was stated that he had been an entirely normal, active child until the middle of September, 1940, when he suffered an attack of severe midabdominal pain. This was relieved by an enema, but it recurred two weeks later, was associated with vomit-

ing, and persisted for eight days. Three weeks later, he again had severe periumbilical pain, and examination revealed mild icterus of the skin, generalized abdominal tenderness, and a palpable mass in the left upper quadrant of the abdomen. He was admitted to a hospital for study.

Hematologic study revealed a red blood cell count of 1,700,000 per cubic millimeter; hemoglobin, 31 per cent; leucocyte count, 11,200 per cubic millimeter, with a normal differential count. The platelet count was 90,600 per cubic millimeter; the bleeding time, nine minutes; and the coagulation time, five minutes. The blood smear showed anisocytosis, polychromatophilia, and the presence of normoblasts. The urine was normal. He was discharged from the hospital with a diagnosis of idiopathic thrombocytopenic purpura.

Seventeen days after this, he again complained of abdominal pain. A few hours later, the child's mother noted that he voided chocolate-colored urine. A second specimen a few hours later was similar in appearance and was examined by a physician who found hemoglobin to be present but no red blood cells. Two days later, the pain was so severe that he was readmitted to the hospital. The blood picture was unchanged. Intravenous pyelography showed no abnormality of the kidneys. He remained six days in the hospital.

Five days after returning to his home, the child awoke at 2:35 A.M. and requested a drink of water. A few moments after lying back in bed, his mother heard him breathing with difficulty, and upon investigating found him totally aphasic and paralyzed on the right side of the body. He was again hospitalized and studied for five weeks.

Examination of the blood during this period showed an erythrocyte count which averaged 2,250,000 per cubic millimeter; hemoglobin, 42 per cent; leucocytes, 8,000 per cubic millimeter. Platelets varied from 52,000 to 150,000 per cubic millimeter. Erythrocyte fragility tests with hypotonic saline solutions were normal. There was no retraction of the blood clot in twenty-four hours. The Kahn test was negative. A blood culture showed no growth.

During this period of hospitalization he seemed to improve somewhat after multiple blood transfusions but suffered so much continual pain in the left upper abdomen that daily injections of morphine were necessary. His paralysis improved little, but there was some recovery of his ability to talk. He was then referred to The Children's Memorial Hospital for further study. The transfer diagnoses remained: idiopathic thrombocytopenic purpura, right hemiplegia, and abdominal pain of unexplained cause.

Past History.—The child was born by normal delivery after a full-term pregnancy. The birth weight was 5 pounds, 15 ounces. He was said to have had measles at 6 weeks of age and mumps at the age of 18 months. He was vaccinated against smallpox in September, 1940.

Family History.—No significant facts were brought out in the family history.

Physical Examination.—Physical examination revealed a well-developed and well-nourished somewhat pale and sallow appearing 5½-year-old boy. There was a noticeable weakness of the muscles of the right side of the face. The tongue protruded to the right side. The heart and lungs were negative. The blood pressure was 136/78. The abdomen was soft and not distended. The liver edge was palpable about one-half inch below the right costal margin and was not tender. The splenic tip was just palpable below the left costal margin. There was some weakness and spasticity of the right arm, and the right leg was totally paralyzed. Muscular atrophy and foot-drop were present. The superficial reflexes were normally active. The deep reflexes were normal on the left side and hyperactive on the right. A positive Babinski reaction and ankle clonus were present on the right.

The following laboratory data were obtained: red blood cells, 3,550,000 per cubic millimeter; hemoglobin, 74 per cent; leucocytes, 8,200 per cubic millimeter; platelets, 46,000 per cubic millimeter; bleeding time, three and one-half minutes; coagulation time, four and one-half minutes. The urine was normal. The Kahn and Wassermann tests were negative. Blood chemistry showed the following results: serum calcium, 10.9 mg. per cent; serum phosphorus, 3.8 mg. per cent; blood cevitamic acid, 1.8 mg. per cent; icterus index, 6.0 units.

The consulting hematologist, Dr. Mila Pierce, made note of several unusual features which seemed untenable with a diagnosis of idiopathic thrombocytopenic purpura. These were the sudden onset of the symptoms after a normal earlier childhood history, occurrence of the jaundice and hemoglobinuria at the onset, and the fluctuating platelet count; it had been observed to reach 150,000 at one time in the other hospital. It was decided to observe the patient and the variations in the platelet count during administration of hesperidin (vitamin P) and ferrous iron orally. The patient was quite comfortable during the four days in the hospital and was discharged to return for blood studies at a later date.

Second Admission.—The child was readmitted to this hospital on April 4, 1941. He had been doing well until two days previously, when he had voided dark brown urine in the morning. His appetite decreased, and his skin and sclerae became slightly icteric. His speech had improved and he had been walking some for a few days.

Examination at this time revealed an icteric tint to the skin and sclerae. There were several petechiae in the skin of the abdomen. A soft-blowing apical systolic murmur was heard on examination of the heart. The spleen was palpable about two and one-half inches below the left costal border.

The blood counts were essentially the same as previously, except that the platelet count was now 36,000 per cubic millimeter. The serum icterus index was 32; the van den Bergh reaction gave a negative direct reaction and a moderate immediate indirect reaction.

The boy was seen again by the consulting hematologist who made note of the moderate thrombocytopenia, incomplete clot retraction, normal bleeding time, and of the slightly microcytic hypochromic type of anemia. She also commented upon the fact that there seemed to be a hemolytic factor present which is not common in idiopathic thrombocytopenic purpura. The patient was seen by a consulting surgeon, Dr. Albert H. Montgomery, who advised splenectomy.

Two days before the operation a transfusion of 225 c.c. of citrated blood was given, using the father who was a compatible donor. There was no adverse reaction. Another transfusion of 100 c.c. from the same donor was given on the morning of the operation. Hemoglobin appeared in the urine after this procedure.

On April 8, 1941, splenectomy was performed by Dr. Montgomery. The spleen was found to be moderately enlarged and rather firmly bound down by adhesions. The immediate postoperative condition was satisfactory. The platelet count rose from 36,000 per cubic millimeter just before the operation to 125,000 per cubic millimeter twenty-four hours later.

Pathologic Report of Spleen.—The spleen measured 3 by 7 by 10 centimeters and weighed 122 Gm.

Microscopic examination revealed malpighian corpuscles which were large and hyperplastic. Moderate fibrosis was present. The sinuses were dilated and appeared almost empty of cells. No megakaryocytes were seen. No hemosiderin was found.

Two days after the splenectomy, the child appeared pale. The bleeding time was normal. The red blood cell count had fallen to 2,400,000 per cubic millimeter, the hemoglobin to 54 per cent, and the platelet count to 96,000 per cubic millimeter. Since hemoglobinuria occurred after the last transfusion, he was given 175 c.c. of

citrated blood from another compatible donor. A chill followed and the patient complained of abdominal pain thirty minutes later, but no hemoglobin appeared in the urine.

During the next ten days, the boy complained of some intermittent abdominal pain and had a low-grade fever, but his general condition seemed satisfactory. His platelet count reached a peak of 362,000 per cubic millimeter six days after the operation. He was discharged to his home on the twelfth postoperative day.

Third Admission.—After arriving home, the child felt well for two days. Then he developed a temperature of 101° F., lost his appetite, and complained of severe pain around the umbilicus during the night. He was readmitted to the hospital on April 24, 1941.

Except for fever, the examination at the time of admission revealed no essential changes from his condition at the time of his last discharge. The blood showed 2,810,000 red blood cells per cubic millimeter, a hemoglobin of 60 per cent, and 16,600 leucocytes per cubic millimeter, with a differential count of 71 neutrophiles, 26 lymphocytes, and 3 monocytes. The platelet count was 125,000 per cubic millimeter. There was one plus albumin in the urine.

Upon the assumption that an infected hematoma might be present in the splenic bed, sulfathiazole was given orally and warm compresses were applied to the abdomen. At first, he complained of occasional attacks of crampy abdominal pain, but the fever and pain subsided and he was discharged from the hospital three days after admission.

Fourth Admission.—During the first six days at home he seemed to be feeling quite well. Then on two successive nights he complained of severe abdominal pain. The parents noted some distention of the abdomen. There was no nausea, vomiting diarrhea, or fever. The urine remained grossly normal. He returned to the hospital on May 8, 1941, and was admitted to the ward medical service.

This time the child appeared quite pale and slightly icteric. The abdomen was markedly distended with fluid. The liver edge was palpable one and one-half inches below the right costal border. The blood picture was unchanged.

It was thought at this time that the ascites might be due to a thrombosis of a branch of the portal vein. No specific therapy was given. The ascites gradually disappeared during the first five days in the hospital, the liver became smaller, and a platelet count taken on May 13, 1941, showed a total of 100,000 platelets per cubic millimeter.

After nine days in the hospital, mild periodic abdominal pain recurred. Four days after the last complaint of such pain, a urine specimen voided at 6:30 A.M. was noted to be very dark brownish red in color. The benzidine test was very strongly positive, but no erythrocytes were found on the microscopic examination. A specimen of urine obtained three hours later was amber in color and gave a negative benzidine reaction. The same was true of two other specimens voided later that day. The icteric tint of the skin and sclerae seemed to have grown more intense. The icteric index was now found to be 25 units.

During the next ten days, there was no further complaint of abdominal pain, but the patient voided specimens of urine at night which contained variable amounts of hemoglobin. The day specimens of urine contained only a minimal amount or were entirely negative for hemoglobin.

Examination of the blood five days after the onset of the hemoglobinuria (May 26, 1941) showed the following: red blood cells, 2,710,000 per cubic millimeter; hemoglobin, 60 per cent; leucocytes, 5,150 per cubic millimeter. The differential leucocyte count showed 41 per cent neutrophiles, 56 per cent lymphocytes, and 3 per cent monocytes. The reticulocyte count was 16.8 per cent, and the platelet count, 382,000.

At this time a presumptive diagnosis of chronic hemolytic anemia with paroxysmal nocturnal hemoglobinuria (Marchiafava-Micheli syndrome) was made, and confirmatory tests were begun according to the methods described by Ham.[4] Chilling of the extremities in ice water did not produce hemoglobinuria. The Donath-Landsteiner test was negative. There were no petechiae produced by the tourniquet test upon the arm.

A fragility test with hypotonic saline solutions was performed in the usual manner. The patient's erythrocytes were found to be normally resistant to hemolysis in such solutions. A similar test of the fragility of the erythrocytes of both of the patient's parents revealed no abnormality.

The method of Bing and Baker as modified by Ham[4] was used for estimations of the plasma hemoglobin. On May 29, 1941, at a time when the nocturnal hemoglobinuria was not particularly marked, the plasma hemoglobin concentration at 10:00 A.M. was found to be 21.8 mg. per cent, while that of a normal control was less than 1.0 mg. per cent.

On June 2, 1941, at 6:00 A.M. a blood sample drawn immediately after the patient awoke showed a plasma hemoglobin concentration of 57.3 mg. per cent, while a sample drawn at 11:00 A.M. of the same day, after the child had been awake for five hours, showed a plasma hemoglobin concentration of 37.0 mg. per cent. Control specimens at both times showed less than 1.0 mg. per cent. A repeat test three days later revealed a plasma hemoglobin concentration of 40.4 mg. per cent in the blood of the patient and less than 1.0 mg. per cent in that of the normal control.

The patient's urine was found to give a positive reaction for hemosiderin granules with the ferrocyanide reagent.

The fragility of the patient's erythrocytes in acidified serum was tested in the manner described by Ham.[4] Washed red blood cells were suspended in the serum of the same blood group which had been acidified by the addition of n/3 hydrochloric acid to produce a pH of approximately 6.5. After incubation at 37° C. for one hour, the patient's cells in acidified serum showed 14 per cent greater hemolysis than did the patient's cells in unacidified serum. The degree of hemolysis of normal control red blood cells was not altered by suspension in the acidified serum.

The same tests with the acidified serum were carried out after inactivation of the serum in a water bath at 56° C. for five minutes. In this case there was no hemolysis of either the cells of the patient or of the normal control. Large amounts of guinea pig complement added to the heat-inactivated serum did not restore its hemolytic activity.

Thus the special in vitro diagnostic tests for chronic hemolytic anemia with paroxysmal nocturnal hemoglobinuria were completed with results which were confirmatory of such a diagnosis.

X-Rays of the Long Bones (June 2, 1941).—The cortex of the long bones was moderately thin, but there was no osteoporosis or subperiosteal absorption present.

The patient improved gradually, the hemoglobinuria subsided, and he was discharged from the hospital on June 5, 1941. His parents were instructed to give him a high vitamin diet, and ferrous sulfate was prescribed.

Fifth Admission.—During the first three weeks at home the child was active and felt very well. Then he developed an alveolar abscess around a carious molar. He developed a fever, his urine began to be dark each morning, and the icterus of the skin and sclerae became more intense. He returned to the hospital on June 28, 1941.

Examination revealed better nutrition than at the time of his last discharge from the hospital. The skin and sclerae were quite icteric, and there was an erythematous rash over the cheeks and the bridge of the nose. There were several carious teeth, and an alveolar abscess of one of the right lower molars was discharging purulent

material. The liver edge was palpable two inches below the costal margin. No ascites was noted. Spasticity of the right arm and leg was still present, and there was shortening of the right tendon of Achilles.

Laboratory data revealed the following: red blood cells, 1,870,000 per cubic millimeter; hemoglobin, 38 per cent; leucocytes, 15,300 per cubic millimeter; platelets, 183,000 per cubic millimeter. The urine voided early in the morning after admission was dark in color and gave a strongly positive benzidine reaction.

The alveolar abscess drained adequately and the fever subsided. Ten days after admission it was noted that the child's urinary bladder was distended and that there was a large urinary residual after voiding. Some tenderness was present over the right kidney and over an area just to the right of the distended urinary bladder. The bladder distention was thought to be due to a neurogenic disorder. Intravenous pyelography showed a normal appearing urinary tract. The tenderness in the right lower abdomen persisted and a mass became palpable. Ascites developed and abdominal pain was present at intervals. Sulfathiazole was given, and the mass decreased in size. The temperature ranged from 101 to 103° F. The fluid in the peritoneal cavity gradually increased in amount.

On July 19, 1941, an exploratory laparotomy was done by Dr. Montgomery. About 750 c.c. of ascitic fluid was found in the abdominal cavity. There was no inflammatory mass found, but a friable grayish exudate was present over the surface of the appendix. The appendix, which was indurated but not acutely inflamed, was removed, and the abdomen was explored. The liver was found to be smooth and grossly normal in appearance. No satisfactory explanation for the formation of the ascites could be found.

Following the operation, the condition of the patient was poor. He was given intravenous fluids, including 75 c.c. of lyophile human serum, and 60 c.c. of whole citrated blood were given intramuscularly. On the next day hemoglobinuria was quite marked. He was then given 150 c.c. of whole citrated blood intravenously on three successive days without reaction or the appearance of hemoglobin in the urine.

Ascites again formed rapidly and to the extent that the patient became quite dyspneic. On Aug. 2, 1941, abdominal paracentesis was performed with removal of 2,300 c.c. of clear, straw-colored fluid which had a specific gravity of 1.008. The ascites reaccumulated rapidly, however, and the patient gained eight pounds in one week.

During this time there had been considerable difficulty in urination, and the amounts voided were quite small. Because of this, mecholyl bromide was given orally in doses of 50 mg. daily. There was an immediate increase in the amount of urine voided and a coincident decrease in the ascites and general improvement in the condition of the patient. Hemoglobinuria continued to occur at intervals and a slight icterus persisted. On Sept. 23, 1941, the red blood cell count was 2,790,000 per cubic millimeter; the hemoglobin was 54 per cent, and the platelets numbered 350,000 per cubic millimeter. At this time it was observed that 12 per cent of the erythrocytes were of the target-cell type.

Mecholyl bromide was continued at a dosage of 100 mg. daily. There was no reaccumulation of ascites, and the bladder seemed to empty normally. The general condition of the patient improved in spite of paroxysms of hemoglobinuria, so that he was discharged from the hospital on Oct. 17, 1941. The mecholyl bromide was continued at home for a time, and the only other medication which was given was a preparation containing vitamins A, B, and D.

Since returning home, the patient has been followed through the hematology clinic of this hospital. He is now getting along quite well in spite of a persistently low erythrocyte count which averages 1,800,000 to 3,000,000 per cubic millimeter. The parents report that he roller skates and carries out most of the activities of a normal

child of his age. There is some residual spasticity of the right arm and leg. It is reported that the urine appears extremely dark in color about three mornings in each month. Mild upper respiratory infections have been noted to provoke such apparent attacks of hemoglobinuria.

DISCUSSION

With this report, another case of chronic hemolytic anemia with paroxysmal nocturnal hemoglobinuria is added to the literature, the first to be reported in a child.

One of the chief points of interest in this patient was the diagnostic problem which was presented. The abdominal complaints associated with fever at the onset of the disease can now be interpreted to be a manifestation of severe intravascular hemolytic reactions. The hemoglobinuria which occurred only one time during the first few months was unfortunately not given proper consideration. As has recently been shown by Ham and Horack,[6] this sign may occur infrequently in proved cases of paroxysmal nocturnal hemoglobinuria.

With the appearance of petechiae, ecchymoses, and a lowered platelet count, a diagnosis of idiopathic thrombocytopenic purpura was made. When the cerebrovascular accident occurred, it was interpreted as being a manifestation of bleeding due to the purpura. While this remains as an unverified possibility, it is well to consider that this may have been a vascular thrombosis, since it is recognized that these are of frequent occurrence in Marchiafava-Micheli's disease.

The platelet count was unusually low in this patient. While thrombocytopenia is recognized to occur in this condition, it has not been previously reported to reach such low levels. Several cases have been reported in which the platelet count was slightly below 100,000 per cubic millimeter. In this case the count reached 35,000 per cubic millimeter just before the splenectomy. The usual increase in the number of platelets occurred immediately after this procedure. The count has been noted to fluctuate through a rather wide range both before and after the operation. There has been no recurrence of the purpuric signs, however, in the year since splenectomy.

The hemolytic factor in the anemia of this patient was recognized early. It was manifest by the persistently low erythrocyte count, the high per cent of reticulocytes, and the mild degree of icterus which was usually present. The first occurrence of hemoglobinuria in this hospital was just after the transfusion of apparently compatible blood. The donor had been used on a previous occasion without reaction, and he was used again at a later date without repetition of hemoglobinuria. In view of the present established diagnosis in this case, it is recognized that this reaction is characteristic of the disease. Hemoglobinuria following the transfusion of compatible blood has frequently been reported, and for this reason this method of treatment is not recommended in combating the profound anemia which is often present.

The presence of ascites was an interesting feature of this case. It first appeared about one month after splenectomy, was associated with abdominal pain, and there was no edema of the extremities or other parts of the body. It persisted for less than a week the first time and did not recur for two months. The second time it was more severe and was associated with fever, abdominal pain, and distention of the urinary bladder. At first it was thought that the ascites may have been the result of a thrombosis of a branch of the portal venous system. This could not be verified at the time of exploratory laparotomy.

The exact cause of the atony of the urinary bladder during the time when the ascites was most marked is not known. The use of the parasympathetic stimulant, mecholyl bromide, seemed to be the factor which brought about normal emptying of the bladder. Coincident with the administration of this drug, there was a very rapid disappearance of the ascites. A more rational explanation for this result of the drug other than its effect in promoting proper emptying of the bladder is not offered.

The inadvisability of performing splenectomy on patients who have this disease has been demonstrated by the records of high mortality and the lack of improvement in those patients who have survived it. In this case, the operation might have been justified as a means of correcting the marked thrombocytopenia even if the complete diagnosis had been known at that time. It was effective in doing this, but the other features of the disease have not been improved.

The observation that hemoglobinuria in this disease is increased with the presence of infection in any part of the body has been demonstrated in this case by its exacerbation at the time when an alveolar abscess was present and during the course of acute upper respiratory infections. It is assumed that the pH of the blood plasma may be altered sufficiently by the disturbance in metabolism brought on by the infection to account for this. It is well to bear in mind that in treating patients with this disease, foci of infecion should be eliminated and that intercurrent infections should be guarded against.

Because of the infrequent occurrence of hemoglobinuria and the obscurity of other features in some cases of this disease which have been reported, it seems that all cases of hemolytic anemia which have any unusual or atypical features should be carefully studied to rule out this diagnosis. The test for fragility of the erythrocytes in acidified serum is easy to perform and is sufficient to identify or exclude the diagnosis of Marchiafava-Micheli syndrome.

SUMMARY

Another case of chronic hemolytic anemia with paroxysmal nocturnal hemoglobinuria is reported. The patient, a child 5 years of age, is the youngest to appear in the literature. Thrombocytopenia was

marked in this case, and purpuric manifestations were present. Splenectomy was performed. The essential features of the disease except the thrombocytopenia were not altered by this treatment.

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IS BREAST MILK ADEQUATE IN MEETING THE THIAMINE REQUIREMENT OF INFANTS?

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FOR several years we have been investigating the metabolism of vitamin B_1 in infants and children. We have wanted to determine the factors which influence thiamine requirements and how adequately these requirements are being met. During the past year this investigation has dealt with the problem of whether breast milk is adequate in meeting the thiamine requirement of young infants. A brief summary of our previous work seems pertinent as an introduction to our breast milk results.

In 1936 we published the results of twenty-three balance studies on preschool children. Since higher amounts of thiamine were retained on higher levels of intake, we had concluded that optimum retention in children of this age required an intake of about 20 units* of thiamine per kilogram of body weight. There are two objections to conclusions based on retention studies. First, we do not know how much of the vitamin is destroyed before the body is able to utilize it. The difference between the amount of thiamine intake and the amount excreted is always large. Second, we do not know the significance of the excreted thiamine. The feces of many children contain at least 50 per cent of the thiamine excreted by them. Studies reported by us in 1939[3] showed that with certain children this fecal thiamine frequently is due to a considerable amount of unabsorbed food thiamine, but there is, of course, the probability that some of it is due to bacterial synthesis. Retention figures for vitamins, therefore, are less reliable in determining requirements than similar data would be in mineral balance studies.

In 1938 two of us (F. W. S. and E. M. K.[2]) published data for two older groups of children whose appetites had been increased when their intake of thiamine had been raised from about 12 to 15 to approximately 18 to 20 units of thiamine per kilogram. This work with older children thus served to confirm the conclusions for the younger children, that possibly 20 units of thiamine per kilogram may be the optimum daily requirement. None of these data gave any evidence in regard to minimum requirements.

In 1940 one of us (E. M. K.[4]) reported a study on the urinary excretion of thiamine in infants aged 1 to 6 months. We had completed a

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*When this study was done, crystalline thiamine was not available, so units, rather than weight, were used as the basis for thiamine measurements. One unit equals 3 μg of thiamine.

series of ninety-eight five-day collection periods on twelve healthy infants whose intakes of thiamine had ranged from 21 to 313 units per day. Since young infants excrete little or no thiamine in their feces, we know that they absorb the thiamine of their milk formulas very completely. Because the vitamin is extremely water soluble, it is readily excreted through the kidneys and the urine content is an index of the amount of thiamine circulating in the body. Surpluses of thiamine are quickly spilled over and eliminated. Thus an extensive study of urinary thiamine should justify conclusions in regard to infant requirements. We found that below 80 units of intake a constantly low quantity of thiamine was excreted in the urine. With intakes of 140 or more units daily, thiamine appeared to be excreted in increasingly larger amounts as higher levels of the vitamin were fed. We suggested on the basis of these data that 80 units might represent the minimum thiamine requirement for an infant in this age period, with 140 units as the maximum amount needed. The requirement for an infant weighing 6 kilograms would thus be between 13 and 23 units per kilogram, which agrees fairly well with our earlier work on older children. These data did not completely satisfy us, however, for we wished to know more specifically what was happening during the metabolism of thiamine, and how the requirement could be met best.

In 1941 two us (F. W. S. and E. M. K.[10]) presented data on blood cocarboxylase. One healthy young infant could not maintain the level of cocarboxylase in his blood on an intake of from 42 to 56 units of thiamine. His blood vitamin decreased steadily until only 1 μg was present per 100 c.c., and it was thought advisable to start thiamine supplements. A second infant, who was exceptionally good in utilizing all nutrients, was just able to maintain the level of his blood cocarboxylase when from 49 to 58 units of thiamine were fed in his formula. The failure of one of these infants to maintain in his blood the vitally important functioning form of thiamine and the success of the other infant in just meeting his need would seem to indicate that we had fed them formulas containing very close to the minimum amount of thiamine required by them. We concluded, therefore, that 60 units of thiamine (10 to 12 units per kilogram) may be a borderline level of intake for young infants. These blood data tend to substantiate the conclusion based on urinary excretion, that 80 units (13 to 16 units per kilogram) represent the minimum requirement.

Throughout all of these studies we had made many analyses of the thiamine content of various kinds of milk. Some of these results were reported in 1939.[9] A more complete summary was presented in 1942.[5] Using biologic and thiochrome methods, we had found that pasteurized milks ranged from 18 to 35 μg of thiamine per 100 c.c. of milk, with an average value of 26 μg. Boiled, pasteurized milk formulas had a slightly lower average of 24 μg of thiamine per 100 c.c. of milk. Evaporated milks ranged from 13 to 27 μg per 100 c.c. of milk reconstituted with

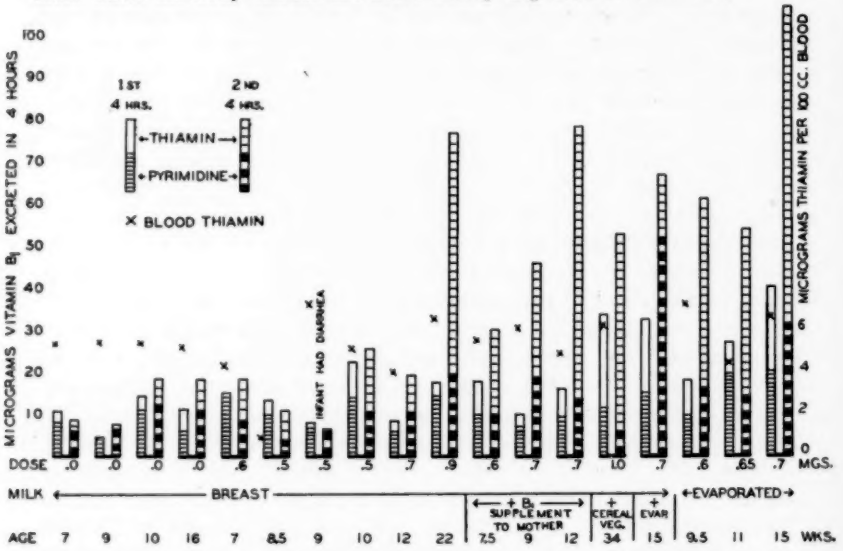
equal parts of water and had an average of 19 μg of thiamine. Breast milks were definitely lower and contained only from 3 to 18 μg, with an average of 9 μg of thiamine per 100 c.c. When these milk values were interpreted in terms of the quantity of milk an infant could consume during a day, it was evident that on many milks the young infant would have difficulty in getting 80 units, or 240 μg, of thiamine each day. It would be quite impossible for an infant to get even 60 units, or 180 μg, of thiamine if he were living exclusively on breast milk and it contained only 10 μg per 100 c.c. Thus either our values for breast milk analyses were too low, or our estimates of an infant's needs were in error, or breast milk frequently is inadequate in supplying the amount of thiamine required by the infant. It seemed necessary for us to study the problem in more detail.

During the past year we have analyzed 111 samples of breast milk from fifty different women. Greater reliability in results than we had previously experienced was obtained by using the microfermentation method of assay which was introduced by Atkin, Schultz, and Frey.[1] An evaluation of methods and the details of our analyses are being presented elsewhere.[6] Our results ranged from 0.6 μg of thiamine per 100 ml. of a sample of colostrum to 36.2 μg per 100 ml. of milk for a woman who had been given intramuscular thiamine. The average thiamine content for all samples was 15.1 μg per 100 ml. It is thus apparent that our previous analyses of breast milk had given us erroneous values below the actual level for most women. This was due in part to the poorer economic group of women which had been studied in our earlier work, and also to the techniques which had been employed.

When our breast milk results were examined more critically, we found that thirty-three women past the neonatal period, whose infants were receiving no other milk than breast milk, had an average thiamine value of 20.1 μg per 100 ml. of milk. In contrast to these results, eight women whose infants required supplementary feedings had an average thiamine content for their breast milk of 9.3 μg.

To aid us in determining whether the breast milk had been adequate in meeting thiamine requirements, we have studied also the urinary excretion of vitamin B_1 by infants living exclusively on breast milk, or on breast milk plus supplementary feedings, or on evaporated milk. The infants were brought to the hospital for two consecutive four-hour collection periods. At the end of the first four-hour period some of the infants received an oral dose of 100 μg of thiamine per kilogram of body weight. By the proper application of tubing, the urine was collected quantitatively directly into a bottle cooled by ice, 25 ml. of 2 per cent glacial acetic acid and toluene being used to preserve the vitamin. Thiamine assays for urine were done by the microfermentation method according to the procedure described in our paper on breast milk.[6] For determining the total vitamin B_1 content, the urine was steam sterilized for thirty minutes and neutralized with sodium hy-

droxide before aliquots were taken for introduction into the fermentation flasks. Pyrimidine was measured after the urine had been treated with sodium sulfite.* Since the thiamine of the urine had been destroyed by the sulfite treatment, its value was calculated by the difference between the total vitamin B_1 content and the pyrimidine. Pollack, Ellenberg, and Dolger[7] have published a report to show that the excretion level of pyrimidine is helpful in evaluating thiamine deficiency since urinary thiamine immediately becomes low when thiamine intake is decreased, whereas urinary excretion of pyrimidine is decreased only later when the body tissues are more nearly depleted of thiamine.


MICROGRAMS VITAMIN B1 EXCRETED IN 4 HOURS
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DOSE .0 .0 .0 .0 .6 .5 .5 .5 .7 .9 .6 .7 .7 1.0 .7 .6 .65 .7 MGS.
MILK ← BREAST → ←EVAPORATED→
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+ CEREAL VEG.
+ EVAP
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Fig. 1.—Urinary excretion of vitamin B_1 by infants. Results for eighteen double collection periods.

The results of eighteen double collection periods on fourteen infants are presented in Fig. 1. It will be seen that both urinary thiamine and pyrimidine values, but especially thiamine levels, were low for most infants receiving breast milk. Many of the infants on unsupplemented breast milk who received test doses of thiamine did not have increased thiamine excretions during the second four-hour period. The average for the first nine infants charted was 3.0 μg of thiamine excreted during the first four hours, and 6.5 μg of thiamine for the second four hours. The only infant on unsupplemented breast milk who excreted significant amounts of vitamin was a 22-week-old infant who presumably was ingesting larger amounts of milk than were taken by the younger infants. He excreted only 3.2 μg of thiamine for the first period, but

*Twenty milliliters of urine and 5 ml. of 4 per cent sodium sulfite were heated in a boiling water bath for thirty minutes, the excess sulfite removed with hydrogen peroxide, and the urine then neutralized with sodium hydroxide.

eliminated 57.1 μg after his test dose of 900 μg of thiamine. Even with this infant, however, the percentage return of the test dose, above the level of thiamine excreted during the first four hours, was only 6.9 per cent.

The pyrimidine excretion of these infants on unsupplemented breast milk was not quite so low as the urinary thiamine. The averages for the group during the two collection periods were 9.0 and 8.4 μg of pyrimidine, respectively, as compared to thiamine values of 3.0 and 6.5 μg. It is of interest that the pyrimidine levels were approximately the same for the first and second period and were not appreciably altered by introduction of the test dose. The fact that the pyrimidine was higher than the thiamine would indicate that these infants were not depleted of thiamine, but their failure to excrete definite increases of thiamine after the test dose would seem to show that they had not been receiving optimal amounts or they would not have kept the test doses within their bodies. We assume that they had been receiving borderline levels of intake.

In contrast to the low results on unsupplemented breast milk, those infants whose mothers had been given some form of vitamin B_1, or those who had had evaporated milk, excreted much higher amounts of vitamin in their urine. The average results were 11.6 μg of thiamine during the first four hours and 41.6 μg of thiamine after the test dose. Pyrimidine values for the two periods were also higher and likewise showed an increase after the test dose. The pyrimidine averages were 12.8 and 20.1 μg for the first and second periods. Since these infants had higher initial excretion levels of thiamine and pyrimidine than did the infants on unsupplemented breast milk, and since they retained less of their test doses, these data tend toward the conclusion that the vitamin B_1 supplements for the mothers or the use of evaporated milk had given the infants a more optimal intake of thiamine. At least their needs seem to have been met more adequately than was experienced with infants on unsupplemented breast milk.

The blood thiamine levels of the infants (Fig. 1) furnished additional proof that the unsupplemented breast milk had been below the optimal in meeting the infant's needs. If we exclude the high blood thiamine level of 7.25 μg per 100 ml. for an infant who had chronic diarrhea and may have been dehydrated, and also exclude the 22-week-old infant who had responded well to his test dose, the average for the remaining seven infants on unsupplemented breast milk was 4.43 μg of thiamine per 100 ml. of blood. Infants who received evaporated milk, or whose mothers had been given vitamin B_1 supplements, had the higher average of 5.83 μg of thiamine in their blood.

Our data for infants fit in well with results reported by Toverud.[11] With improved thiochrome technique she was unable to detect thiamine in the urine of breast-fed infants except in one or two cases where thiamine supplements had been used. Our method of analysis is more

sensitive than hers, but we would expect urinary thiamine to be lower in her group since the average thiamine content of breast milk reported by her was only 10.8 μg per 100 ml. in contrast to the average of 20.1 μg per cent for the milk of our mothers who were past the neonatal period and did not need to give their infants supplementary formulas.

The breast-fed infants summarized in Fig. 1 had received milk containing about 20 μg of thiamine per 100 ml. If the infants took an average of one ounce of breast milk per kilogram at each feeding, their thiamine intakes would have been 150 μg daily for an infant weighing 5 kilograms, 180 μg for an infant weighing 6 kilograms, and 210 μg for an infant weighing 7 kilograms. Since the urinary thiamine of these infants would seem to indicate that they had received borderline levels of intake, the results of the present investigation would tend to verify our earlier conclusion that about 200 μg of thiamine are the minimum requirement of a young infant. The 22-week-old infant who excreted more of his test dose than did other breast-fed infants had received approximately 325 μg of thiamine, or about 36 μg per kilogram. The optimum thiamine requirement for young infants is probably, therefore, not quite as high as our suggestion of 20 units (60 μg) per kilogram for children but may well be in the neighborhood of 40 μg per kilogram.

The obvious conclusion to our breast milk studies would appear to be that if a woman wishes to nurse her infant successfully, she must take special precautions to insure that she receives a thiamine intake which is adequate for her specific needs. Some women can do this by means of well-chosen foods; others require thiamine supplements. Her breast milk should contain at least 20 μg of thiamine per 100 ml. If the infant is small or weak and unable to take satisfactory amounts of breast milk, or if he has an increased need because of losses due to diarrhea, thiamine therapy is advisable.

SUMMARY

1. Thiamine and pyrimidine have been determined by microfermentation technique in eighteen double collection periods, of four hours each, for fourteen infants.

2. Nine infants receiving unsupplemented breast milk excreted 3.0 μg of thiamine and 9.0 μg of pyrimidine during the first four hours and 6.5 μg of thiamine and 8.4 μg of pyrimidine during the second four hours. The administration of a test thiamine dose between the two periods did not affect the results materially. These infants had received breast milk containing about 20 μg of thiamine per 100 ml., which gave them daily intakes, depending on their size, of between 150 and 210 μg of thiamine.

3. One 22-week-old infant on unsupplemented breast milk excreted 37.1 μg of thiamine after his test dose, as compared to 3.2 μg during

the first four hours. He had received milk containing about 23.5 μg of thiamine per 100 ml. to give him an intake of approximately 325 μg of thiamine.

4. Eight infants whose mothers had received vitamin B_1 supplements, or who had been given evaporated milk formulas, excreted larger amounts of both thiamine and pyrimidine than did the unsupplemented breast-fed infants. Averages of 11.6 and 41.6 μg of thiamine and 12.8 and 20.1 μg of pyrimidine were found for the first and second four-hour periods, showing that these infants had not needed to retain their test doses as had the other group of infants.

5. It was concluded that young infants appear to have a minimum thiamine requirement of approximately 200 μg daily. This can just be met by the normal healthy infant if his mother's milk contains 20 or more μg of thiamine per 100 ml. The suggestion is made that 40 μg of thiamine per kilogram may be a practical standard to cover the ordinary needs of the young infant.

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THE DIAGNOSIS AND EVALUATION OF COMPENSATED AND UNCOMPENSATED PATENCY OF THE DUCTUS ARTERIOSUS

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SINCE the first successful ligation of a patent ductus arteriosus in 1938,[1] there has been widespread appreciation of the practical importance of differentiating this from other defects of the heart and great vessels. The large number of patients who have undergone surgical treatment has offered an unusual opportunity to check the diagnosis on the operating table and to learn more of the pathologic physiology. As a result of this experience it has become apparent that an accurate and trustworthy differential diagnosis is possible. Furthermore, by proper evaluation of the clinical signs a distinction can be made between the cases in which the arteriovenous shunt is small and those in which it is large.

THE MURMUR AS RECORDED BY THE PHONOCARDIOGRAM

The murmur of a patent ductus arteriosus is its most distinctive feature. With it, a reliable diagnosis can be made, even in the absence of any other sign or symptom. Without it, a reliable diagnosis cannot be made. It is a loud, coarse, low-frequency murmur, crescendo during systole, reaching a maximum intensity at the time of the second sound, and decrescendo during diastole (Fig. 1). When it extends from the beginning of systole to the end of diastole, as it usually does, it may be described as continuous. Not infrequently, however, it disappears during late diastole so that there is a quiet period before the first sound (Figs. 1*G*, 2*B*, 3*A*). In such instances the first sound can be heard separately. The second sound may be accentuated (Fig. 1*E*) or entirely obscured by the murmur.

The maximal intensity of the murmur is over the pulmonic area to the left of the sternum in the second interspace. From here it may be transmitted to the apex, the axilla, and widely over the whole chest. It is not transmitted with much intensity into the great vessels of the neck. The murmur may diminish to a surprising degree following forced, sustained inspiration, but in so doing maintains its maximal intensity at the time of the second sound and its continuation into diastole (Fig. 2).

The characteristic features of the murmur can be clearly illustrated by the phonocardiogram which serves to corroborate clinical appraisal and to record the murmur permanently. Since a reliable diagnosis can usually be made from the murmur, it follows that the phonocardiogram is of diagnostic value. Records such as those shown in Figs. 1 to 3 are so distinctive as to permit a diagnosis from examination of the tracing alone.

From the Children's Hospital and Infant's Hospital, Boston, and the Department of Pediatrics, Harvard Medical School.

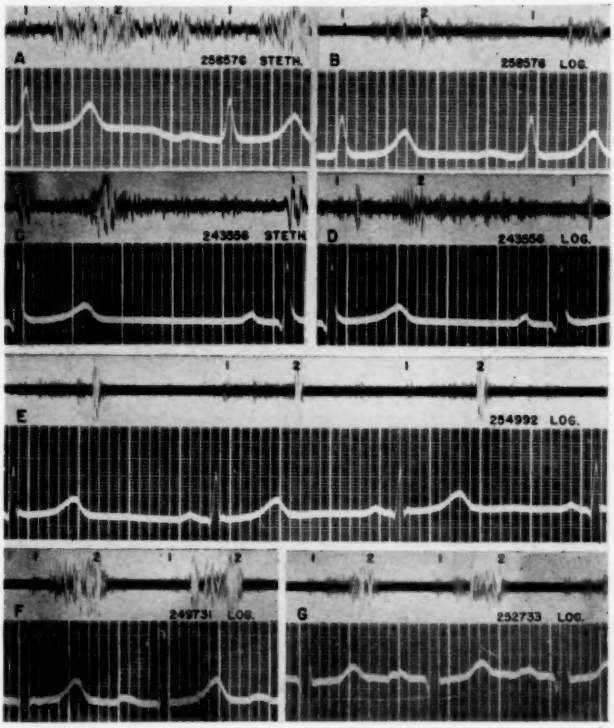

Fig. 1.—Representative phonocardiograms of patent ductus arteriosus. All diagnoses were proved surgically. The microphone was placed over the pulmonic area at the location of the maximal intensity of the murmur. Each record is labelled according to whether the stethoscopic or logarithmic microphone was used. (The technical details have been described by Rappaport and Sprague.[16]) *A* and *B* are from one patient, *C* and *D* from another, showing the comparison between the two microphones.

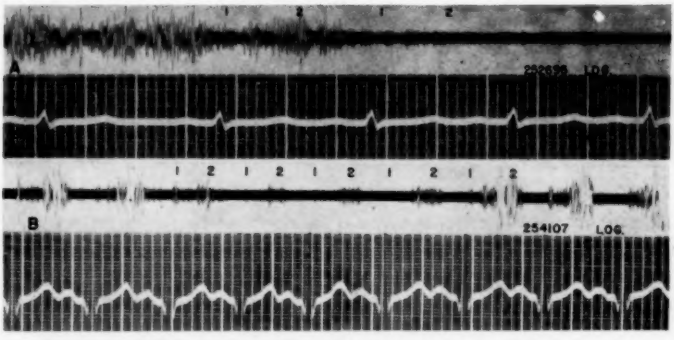

Fig. 2.—Phonocardiograms of patent ductus arteriosus showing decreased intensity of the murmur during inspiration. *A*, Before and during forced inspiration; *B*, 10-month-old infant, showing variation during normal respiration with the murmur decreasing during inspiration. Diagnosis proved surgically at 11 months of age.

It is sometimes said that a patent ductus arteriosus may have only a systolic murmur. This statement is supported primarily by the statistical summary of Abbott.[2] In her *Atlas of Congenital Cardiac Disease* she has listed ninety-two case reports describing patency of the ductus arteriosus uncomplicated by associated anomalies. Nineteen of these were infants, only one of whom had a murmur which was noted to extend into diastole.* Even with considerable experience it is very difficult to determine whether a murmur in the rapidly beating heart of an infant is purely systolic or whether it may also extend into diastole. Occasional proved cases have been observed in older children where the murmur has been described as systolic when first observed and only later developed the characteristic continuous quality. Careful scrutiny of these cases leaves room for doubt about the description of the murmur.

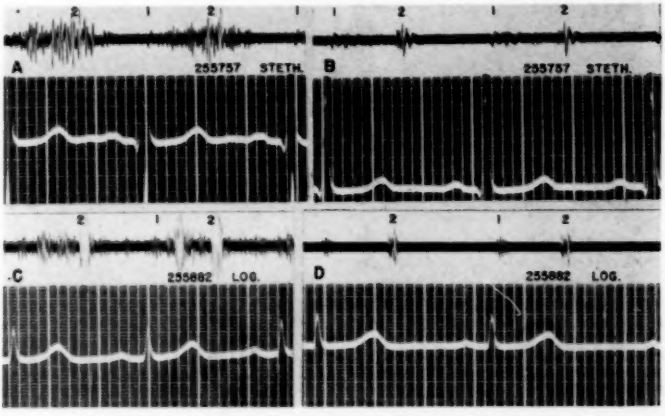

Fig. 3.—Phonocardiograms of two patients with patent ductus arteriosus before (*A* and *C*) and after (*B* and *D*) surgical ligation.

There is still much to be learned about the evolution of a patent ductus. Why does the ductus sometimes fail to close and when can its patency be considered pathologic? What is the explanation for the apparent failure to find any murmur in infants who later develop characteristic murmurs? Pending clarification of these points, experience dictates that the soundest policy is to make a diagnosis of a patent ductus only in the presence of a murmur which extends into diastole.

A recent case, of particular value in relation to the interpretation of physical signs in infancy, is a baby who was first examined in the Children's Hospital clinic at the age of 5 months. At that time there was a loud murmur maximal over the base of the heart to the left of the sternum. Opinion varied among several well-trained observers as to whether the murmur was purely systolic or extended also into diastole.

*This information, which does not appear in the published statistics, is based upon a personal review of the data, permission for which was generously given by Dr. Abbott.

A phonocardiogram showed a murmur typical of patency of the ductus (Fig. 2*B*). A diagnosis of patent ductus was therefore made, and this was confirmed a few months later by surgical ligation. This case is also noteworthy because of the early age at which severe congestive failure developed (before 5 months) and the early age of surgical ligation (11 months).

In patency of the ductus arteriosus, a prominent thrill is usually felt over the pulmonic area. It has the same diagnostic significance as the murmur, for it indicates that the vibrations are low enough in frequency and great enough in intensity to allow them to be palpable as well as audible. If the murmur is loud and continuous, there will be a correspondingly prominent continuous thrill. If the murmur is less prominent, the thrill may be felt only at the time of the second sound.

At the time of operation there has been opportunity to palpate the exposed great vessels directly. The thrill appeared to arise mostly from the ductus and the adjacent portion of the pulmonary artery. This suggests that the thrill and hence the murmur result from the vibrations caused by the swirling of arterial blood rushing into the pulmonary circuit. Following satisfactory closure of the ductus and obliteration of these abnormal currents, the thrill and murmur disappear (Fig. 3).

COMPENSATED VERSUS UNCOMPENSATED PATENT DUCTUS ARTERIOSUS

A patent ductus arteriosus forms an arteriovenous communication allowing blood to flow from the aorta, through the ductus, into the pulmonary artery. This results in a leak which in many aspects is similar to the more familiar aortic regurgitation due to incompetent valves. It is customary to describe aortic regurgitation as "early" or "free," according to the degree of regurgitation indicated by the absence or presence of an effect on the peripheral circulation. "Early" aortic regurgitation has no peripheral signs. It is diagnosed by a high-pitched murmur directly following the second sound heard best along the left sternal border in the third interspace. "Free" aortic regurgitation, on the other hand, has in addition to the murmur a low diastolic pressure, wide pulse pressure, collapsing pulse, and capillary pulsation.

A similar helpful differentiation can be made in cases of patent ductus arteriosus. When there is a relatively small arteriovenous shunt, the heart may become well adjusted to the mechanical handicap, so that there may be no apparent circulatory embarrassment. In such cases, the heart hypertrophies little, if at all. The diastolic pressure is maintained at a normal level or is only slightly below normal. There are no peripheral signs of regurgitation. The circulation is adequate to allow normal growth and development of the child. There is no apparent limitation of cardiac reserve. These patients may live active and long lives.[3, 4, 5] Dr. Burton Hamilton has recently shown me a patient with a patent ductus who is a vigorous, active man at the present age of 73. Other patients have successfully had multiple pregnancies.[6, 7] For the patients

who show no indications of an impaired circulation, the term *compensated patent ductus arteriosus* is suggested. They may be diagnosed by the distinctive murmur in the absence of all other signs or symptoms.

When, on the other hand, there is evidence of a shunt large enough to throw an undue burden on the heart, the term *uncompensated patent ductus arteriosus* may be used. Here, in addition to the characteristic murmur, there are other signs and symptoms which are of value in estimating the size of the ductus and the severity of the circulatory disturbance. The most important of these is a lowering of the diastolic pressure, resulting in the familiar peripheral signs of aortic regurgitation: wide pulse pressure, collapsing pulse, and capillary pulsation. The level of the diastolic pressure serves as a guide to the magnitude of the shunt: the lower the diastolic pressure and the greater the pulse pressure, the greater the amount of blood flowing through the ductus. Following exercise, the pulse pressure may be further increased by a

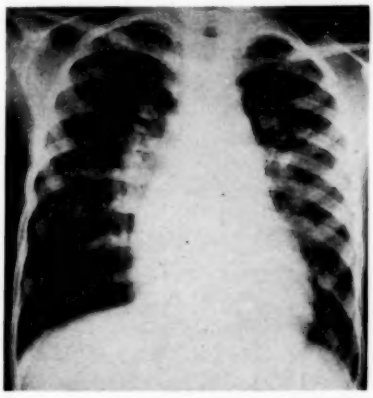

Fig. 4.—Roentgenogram of chest of patient with patent ductus arteriosus showing pulmonary congestion. (C. H., 157588.)

fall in the diastolic pressure associated with a less significant rise in the systolic pressure. In severe cases the diastolic pressure may be zero even at rest.

When the systemic circulation is impaired in childhood, retardation of physical development may result. This is well illustrated by some of the children who have been operated upon. They have been underweight and of a thin ptotic type. The fact that their failure to gain properly has been related to an abnormal circulation is substantiated by the rapidity of gain following operation.[8]

The effect on the pulmonary circuit of an excess volume of blood thrown into it by a large ductus is an increase in the pulmonary arterial pressure and pulmonary congestion. This latter is best determined roentgenographically and may be quite marked (Fig. 4).

The combined effect of the handicap under which the left ventricle is working and the extra load which the right ventricle has to overcome is that both right and left ventricles hypertrophy. The heart may become greatly enlarged, but there is little, if any, preponderance of one side over the other. Therefore, the electrical axis is usually normal or deviated only slightly to the right or left.

When the heart is severely overburdened, congestive failure may ensue. This is accompanied by the usual signs and symptoms of insufficiency, dyspnea and orthopnea sometimes becoming marked. Cyanosis may occur, as in any patient with congestive failure, but it does not become the deep cyanosis associated with the defects which allow venous blood to mix with the arterial. It is therefore misleading to accept Abbott's classification[2] and place patent ductus arteriosus in the group of congenital defects with latent cyanosis.

The pathologic physiology upon which these signs and symptoms depend has recently been clearly demonstrated by the work of Eppinger, Burwell, and Gross.[9] By taking samples of blood directly from the aorta and pulmonary artery at the time of operation, they showed that in the patients studied, and under the conditions of a surgical operation, the flow of blood from aorta to pulmonary artery was as much as 45 to 75 per cent of all the blood pumped into the aorta by the left ventricle. In these patients the left ventricle expelled from two to four times the volume of blood expelled by the right ventricle in a given period of time. These studies, which were supported by similar observations in dogs with an artificial aortopulmonary communication, show very clearly the excessive cardiac burden which can result from a large ductus. It is well to remember that the patients from whom these values were obtained were cases selected for surgery because of evidence of an uncompensated ductus arteriosus. It is not fair to conclude therefore that a comparable increase in the work of the heart results from a small shunt and a compensated ductus.

DIFFERENTIAL DIAGNOSIS

A patent ductus arteriosus may be associated with other congenital anomalies of the heart or great vessels and may then present a difficult problem in differential diagnosis. However, this discussion is concerned only with patency of the ductus as an uncomplicated defect, and in these cases the diagnosis is usually easy and reliable (Table I). Cyanosis and clubbing are absent, which at once excludes a large group of more severe malformations such as those related to malrotation of the great vessels. The murmur is distinctive enough to be of diagnostic value entirely by itself. When, in addition to the murmur, there are the associated signs of an uncompensated ductus, diagnosis becomes positive. The electrocardiogram is helpful in that it should be free of any marked axis deviation. There may be slight deviation to the right or left but a marked shift, particularly to the right, suggests other or associated anomalies.

Roentgenographic examination may or may not be helpful. A prominence in the region of the pulmonary artery is often described as characteristic of a patent ductus. If present, this is a suggestive sign, but actually in children it is usually slight or altogether absent. In the presence of an uncompensated ductus, there may be enlargement of the heart, exaggerated cardiac pulsation, and a considerable degree of pulmonary congestion in the hilar regions.

TABLE I

SUMMARY OF DIFFERENTIAL DIAGNOSIS OF COMPENSATED AND UNCOMPENSATED PATENT DUCTUS ARTERIOSUS, INTERVENTRICULAR SEPTAL DEFECT, INTERAURICULAR SEPTAL DEFECT, AND PULMONARY STENOSIS

	PATENT DUCTUS ARTERIOSUS		I-V SEPTAL DEFECT	I-A SEPTAL DEFECT	PULMONARY STENOSIS
	COMPENSATED	UNCOMPENSATED			
Cyanosis	Absent	Absent*	Absent*	Absent*	Usually marked
Clubbing	Absent	Absent	Absent	Absent	Present
Murmur	Systolic crescendo; diastolic decrescendo		Systolic	Systolic† (sometimes absent)	Systolic
Location of maximal murmur	Pulmonic area		Sternal border in third and fourth interspaces	Pulmonic area	Pulmonic area
Diastolic blood pressure	Normal or slightly low	Low	Normal	Normal	Normal
Pulmonary congestion	None or slight	Prominent	Absent	Prominent	Absent
EKG-Axis deviation	None or slight right or left		None	Marked right	Right

*Cyanosis may be present due to congestive failure.
†Pulmonic incompetence may be present and cause an early diastolic murmur.

An *interventricular septal defect* should be readily distinguished by the nature of the murmur which is limited sharply to systole and maximal in the third and fourth interspaces along the left sternal border (Fig. 5). The electrocardiogram usually shows no significant axis deviation. A deep S wave in the standard Leads I and II is usually present.[10] In certain patients in whom the diagnosis of patent ductus arteriosus has been made, it has seemed impossible to exclude an associated interventricular septal defect, the signs of which might be obscured by a louder ductus murmur.

An *interauricular septal defect* may give symptoms and signs quite similar to the patent ductus. The characteristic features of this anomaly have recently been described by Taussig, Harvey, and Follis,[11] and by Bedford, Papp, and Parkinson.[12] The roentgenogram may simulate that of a patent ductus arteriosus. Both malformations may be associated with enlargement of the pulmonary artery and hilar congestion. Roesler[13] and Taussig and co-workers[11] have shown that there is often an associated mital stenosis. These patients are free from the left

auricular enlargement commonly resulting from mitral stenosis, for here the strain in the left auricle is relieved by the defect in the septum. The murmur of an interauricular defect is subjected to great variation. It may be altogether lacking. Usually, however, there is a prominent systolic murmur and thrill maximal over the pulmonic area (Fig. 6). An early diastolic murmur occurs in some cases, due presumably to pulmonary incompetence. This combination of murmurs is quite different from the characteristic murmur of a patent ductus. A feature which may be helpful in the differential diagnosis is the right axis deviation usually present in an interauricular septal defect.

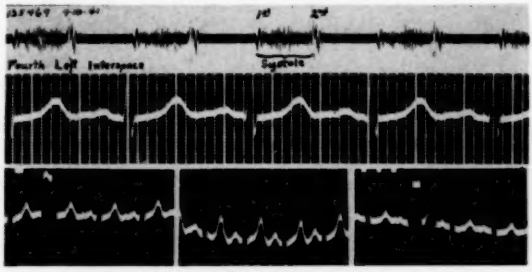

Fig. 5.—Interventricular septal defect. Microphone placed at fourth left interspace. Murmur is sharply limited to systole. Electrocardiogram shows negative S waves in the three standard leads. (C. H., 135469.)

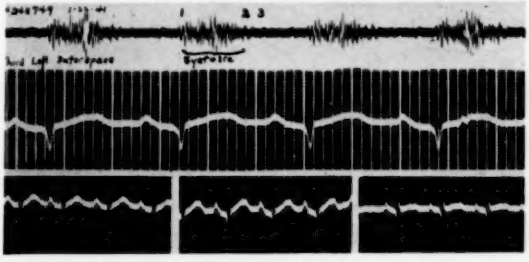

Fig. 6.—Interauricular septal defect. Microphone placed at third left interspace. Murmur limited to systole. Prominent right axis deviation. (C. H., 248749.)

Coarctation of the aorta should be readily differentiated by finding the blood pressure in the arms higher than in the legs, as determined by the sphygmomanometer or palpation of femoral, popliteal, or dorsalis pedis arteries. Evidence of collateral circulation may be found in forcible pulsation in dilated tortuous arteries over the back and the appearance, roentgenographically, of erosion of the ribs from pressure by enlarged intercostal arteries.

Pulmonic stenosis is usually associated with malrotation of the great vessels and most frequently found in the combination of defects constituting the tetralogy of Fallot. These are distinguished by deep cyanosis. Rarely, pulmonary stenosis occurs alone and without cyanosis,

in which case the identifying features should be a systolic murmur, enlargement of the right ventricle with marked right axis deviation, and high P waves in the electrocardiogram.

A *venous hum* in the great veins of the neck is a common finding in normal children which is often overlooked. This is purely functional and has no pathologic significance but is sometimes a source of confusion. It causes a continuous murmur which may be fairly loud and associated with a thrill maximal just above the clavicle (Fig. 7). Sometimes it is transmitted below the clavicle and over the pulmonic area. It is usually best heard on the right but may also be heard on the left. A change in position from the upright to the prone position may cause the murmur to diminish or altogether disappear.

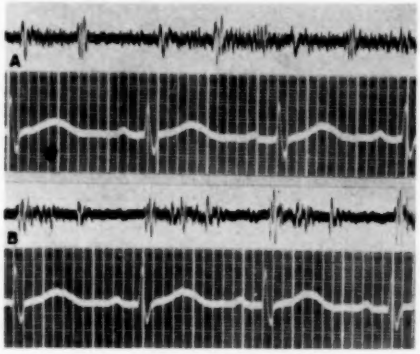

Fig. 7.—Venous hum (C. H., 258810). *A*, Microphone placed in right supraclavicular area showing coarse continuous murmur; *B*, microphone placed over pulmonic area showing transmission of murmur.

SHOULD THE COMPENSATED AS WELL AS THE UNCOMPENSATED DUCT BE LIGATED?

In an earlier communication[14] the statement was made that surgery should be advised only for those patients who had evidence of a large shunt; that is, for those whose condition the term uncompensated ductus is now suggested. For these patients, ligation in the hands of well-trained surgeons has now been established as a beneficial and sometimes lifesaving procedure.

It is still an open question as to whether ligation should be advised for compensated as well as uncompensated patency of the ductus. The main reason for doing so would be to prevent the development of subacute bacterial endarteritis or endocarditis. The incidence of this complication is still unknown. As pointed out earlier, a fair statistical incidence cannot be derived from a compilation of isolated case reports. From this point of view the oft-quoted 25 per cent incidence taken from an analysis of Abbott's chart[2] or the 50 per cent incidence suggested by Bullock, Jones, and Dolley[15] is open to criticism. Furthermore, although

there is reason to hope that a ligated ductus will remain free of bacterial vegetations, sufficient time has not yet elapsed to allow proof of this. Until further experience has accumulated, it appears wise to pursue a policy of watchful waiting for a compensated ductus and to advise ligation whenever evidence of an uncompensated ductus appears. The fact that ligation has been successfully performed within the first year of life indicates that the optimal time for surgical intervention is not related to any particular age but rather to the presence or absence of signs of an overburdened circulation.

SUMMARY

The term compensated patent ductus arteriosus is suggested for the condition of those patients in whom the arteriovenous shunt is small and there is no appreciable effect on the peripheral circulation or cardiac reserve. Such cases may be reliably diagnosed by the characteristic murmur in the absence of any other sign or symptom. The murmur, as illustrated by the phonocardiogram, is crescendo in systole, continues into diastole, becoming decrescendo.

The term uncompensated patent ductus arteriosus may be used for those patients having a large arteriovenous shunt with evidence of present or impending circulatory insufficiency. In such cases, in addition to the characteristic murmur, there is a low diastolic pressure with the peripheral signs of aortic regurgitation, cardiac enlargement, pulmonary congestion, and impaired growth and development of the child. These cases may be compared to "free" aortic regurgitation.

Surgical ligation is indicated for the uncompensated patent ductus arteriosus at whatever age signs of circulatory embarrassment appear. For patients with a compensated ductus, a policy of watchful waiting is advised.

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THE ROLE OF COLON ORGANISMS AND THEIR TOXINS IN EPIDEMIC DIARRHEA OF THE NEWBORN INFANT

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EPIDEMICS of infectious diarrhea of the newborn infant have been occurring in the Province of Ontario. Four epidemics are described together with the bacteriologic findings in each outbreak. From two hospitals experiments have been carried out on the toxin production of different strains of colon and paracolon organisms isolated from the tissues of fatal cases and from the stools of affected infants.

HOSPITAL A

Epidemiology.—There were two outbreaks in this nursery. The first occurred in December, 1940. On December 3 one infant, 5 days of age, began to have loose stools, vomited, and lost weight rapidly. The infant was given interstitial injections of saline and recovered. From December 3 to December 15 there were sixty-two infants in the nursery and twenty-six of them were definitely ill. All the infants were discharged from the hospital, although some of them still had loose watery stools. Four of these infants were readmitted to the pediatric ward, four, seven, eighteen and twenty days after discharge. Three of them died. The diagnosis was infectious intoxication. No autopsies were performed.

A second mild outbreak occurred in February, 1942. There were thirty-one infants in the nursery and seven had loose stools while one had sore buttocks. There was no abnormal loss of weight and no fever.

Bacteriology.—In the first epidemic in December, 1940, rectal swabs and fecal specimens showed the following:

16 sick infants in the nursery	Hemolytic colon in 14
3 well infants in the same nursery	No hemolytic colon
Nursery supervisor who made the formulas	Hemolytic colon present
No salmonella or paracolon organisms were isolated	

During the second outbreak in February, 1942, anal swabs from the infants showed the following:

8 infants with loose watery stools	Hemolytic colon in 7
2 infants with loose stools but not tested for hemolytic colon	Paracolon in 2
16 normal infants in the same nursery	Nonhemolytic colon in 11
	No colon organisms in 5

Samples taken from the quart bottles of complementary feeding made for twenty-four hours showed a high bacterial count with the presence of nonhemolytic colon organisms. The bathing table, after the infants had been changed on it, showed the presence of hemolytic colon. Stool

specimens from seventeen of the nursing staff had the following: paracolon organisms in two nurses; four different strains of hemolytic colon in four nurses.

Six of the hemolytic colon organisms from the infants, the strain from the bathing table, and a strain from one of the night nurses were identical by their sugar reactions. One strain from an infant and one from a nurse were identical. Only one of the mothers with affected babies had a hemolytic colon present in her stool, and it was different from the common strain in the infants.

HOSPITAL B

Epidemiology.—On May 6, 1941, an infant developed infectious diarrhea, and the baby's mother had diarrhea at the same time. The infant was given a blood transfusion and recovered. One week later another infant became ill with similar symptoms. From May 6 to May 25 seven infants were definitely ill and one of them died. Protein milk was being given as a complementary feeding, and the infants who had more of this feeding were more severely ill.

Bacteriology and Pathology.—An autopsy was performed on the infant who died, and there was a bronchopneumonia with some enteritis. Two weeks later, after the epidemic had subsided, an examination of stool specimens of the infants in the hospital showed the following:

6 well babies (breast and bottle fed)	Hemolytic colon in 2
6 bottle-fed babies	Hemolytic colon in 5
9 sick babies in the pediatric ward who had not been in the nursery	Hemolytic colon in 2

No Salmonella or paracolon organisms were present.

HOSPITAL C

Epidemiology.—During October, 1941, twelve infants in the nursery were sick. Two of them were transferred to the pediatric ward and had infectious intoxication. Ten of the sick infants were in the nursery for three-hour feedings while only two were in the nursery for four-hour feedings. The babies in the three-hour feeding nursery were smaller and received a greater amount of the complementary feedings.

Bacteriology.—The evaporated milk formula made for twenty-four hours and the nipple jar showed an abundant growth of hemolytic colon organisms. No feces samples were examined.

HOSPITAL D

Epidemiology.—The outbreak in this hospital was severe, and the epidemic was not controlled until the obstetrical unit was closed.

The sick infants showed the characteristic symptoms of listlessness, severe diarrhea, rapid loss of weight, abdominal distention, dehydration, and severe intoxication. Most of the infants had no fever. As pre-

mature infants were the first to become ill and die, it was not until a normal infant died that the hospital staff realized that there was an epidemic in the nursery. Six of the twelve infants who died were premature.

Period of the Epidemic From April 8 to May 12, 1941	
Babies in the nursery during this time	53
Babies discharged as normal	44
Babies who showed symptoms while in the nursery	9, of whom 7 died
Babies who were discharged and readmitted later	9, of whom 5 died

The infants who were readmitted had a somewhat different clinical picture. The temperature was more elevated, and there were signs of bronchopneumonia. In all infants the urine showed albumen and sugar, but red blood cells and casts were rare.

Pathology.—Autopsies were performed on four infants. In three infants dying thirteen, fourteen, and eighteen days after birth, there was an acute bronchopneumonia with some congestion of the organs, and one infant had otitis media. The fourth infant died nine days after birth, and there was some congestion of the organs but no other definite pathologic lesions.

Bacteriology.—No dysentery or Salmonella organisms were isolated from feces specimens before death or from the organs or heart blood after death.

Two organisms were more prevalent in the stools of the sick infants. They were hemolytic colon and paracolon (late lactose fermenter). Both these organisms were hemolytic for sheep blood cells on blood agar plates.

The organisms isolated from the infants' feces are shown in Table I.

TABLE I

INCIDENCE OF HEMOLYTIC COLON AND PARACOLON IN THE FECES OF INFANTS IN HOSPITAL D

	NUMBER EXAMINED	HEMOLYTIC COLON	HEMOLYTIC PARACOLON
Fatal cases	5	4	4
Sick infants in the nursery	6	4	6
Well infants in the same nursery	5	1	1
Well infants in another hospital with no epidemic	13	1	7
Adults in an area not connected with the sick infants	20	3	1

BIOLOGIC CHARACTERISTICS OF COLON AND PARACOLON ORGANISMS ISOLATED FROM THE FECES OF INFANTS IN HOSPITAL A AND HOSPITAL D

Hospital A.—In a mild outbreak which occurred in this nursery in February, 1942, the following organisms were isolated:

Strain E: Hemolytic colon isolated from six out of eight infants with loose stools; this organism was also obtained from the bathing table and from the stool of a night nurse

Strain F: Nonhemolytic colon which was common to most of the normal infants

Strain G, Strain H: Paracolon organisms isolated from two infants with loose stools

The biologic reactions of these various strains are recorded in Table II.

TABLE II

SUGAR REACTION OF DIFFERENT STRAINS OF COLON AND PARACOLON ORGANISMS ISOLATED FROM INFANTS

STRAIN	DEXTROSE	SACCHAROSE	LACTOSE	MANNITE	SALICIN	MALTOSE	XYLOSE	ARABINOSE	INOSITE	DULCITE	RHAMNOSE	LITMUS MILK	INDOL	HEMOLYSIS
A	ag	-	ag	ag	-	ag	-	ag	-	ag	ag	ac	+	+
B	ag	ag	ag	ag	ag	ag	ag	ag	-	ag	ag	ac	+	+
C	ag	-	ag 2-4	ag	ag	ag	ag	ag	-	ag	ag	ac	+	+
D	ag	ag	ag	ag	-	-	ag	a	-	ag	ag	ac	+	-
E	ag	ag	ag	ag	ag4	ag	ag	ag	-	ag	ag	ac	+	+
F	ag	-	ag	ag	ag	ag	ag	ag	-	ag	ag	ac	+	-
G	ag	ag	ag3	ag	ag	ag	ag	ag	-	-	ag	ac	±	+
H	ag	ag	ag4	ag	ag	ag	ag	ag	-	ag	ag	a(c-8)	+	+

Strains A, B, and E, hemolytic colon; Strains C, G, and H, paracolon; Strains D and F, nonhemolytic colon.

Hospital D.—At the time of the epidemic in April, 1941, no special work was done on the hemolytic colon organisms, and they were recorded only as being present or absent in a specimen. The tissues of one of the infants were preserved in the frozen state in carbon dioxide snow. This infant died nine days after birth and showed very few pathologic lesions. Seven months later the frozen tissues of this infant were cultured and the following organisms isolated:

Strain A: Hemolytic colon from kidney tissue
Strain B: Hemolytic colon from brain tissue
Strain C: Hemolytic paracolon from kidney tissue
Strain D: Nonhemolytic colon from lung tissue

When the top of a colony of paracolon (Strain C) several days old was streaked on an endo plate, colonies were produced which took different periods of time to ferment lactose. These would appear to be similar to those organisms classified as *Escherichia coli* mutabile.[1, 2] This strain did not ferment saccharose.

Cultures of the Strains A, B, and C injected intraabdominally into mice were lethal in twelve hours, while Strain D was lethal in thirty-six hours.

FEEDING EXPERIMENTS WITH COLON ORGANISMS ISOLATED FROM SICK INFANTS

Cats.—One old cat and three kittens were fed live cultures of Strain A (hemolytic colon) in milk, morning and evening, for two days. The

TABLE III

INTRA-ABDOMINAL INJECTIONS INTO CATS OF DIFFERENT STRAINS OF COLON AND PARACOLON TOXINS PRODUCED BY GROWING ORGANISMS IN 10 PER CENT CARBON DIOXIDE AND 90 PER CENT AIR

STRAIN		SYMPTOMS (MINUTES ELAPSING BEFORE ONSET OF SYMPTOMS)		PATHOGENICITY	RECOVERY OR DEATH
		DIARRHEA	VOMITING		
A (Hemolytic colon from fatal case)					
Unheated:	Cat 1	–	2, 25	++++	D (18 hours)
	Cat 2	–	–	–	–
	Cat 3	–	–	+	R (Few hours)
	Cat 4	70	45, 55	++	R (24 hours)
Heated:	Cat 1	–	–		–
	Cat 2	25	40, 55	++	R (24 hours)
Boiled:	Cat 1	–	25	++++	D (6 days)
	Cat 2	–	–	–	–
	Cat 3	5	25, 30, 35	+++	R (3 days)
	Cat 4	–	55	++	R (18 hours)
	Cat 5	–	–	+	R (Few hours)
B (Hemolytic colon from fatal case)					
Unheated:	Cat 1	–	45	++++	D (36 hours)
Heated:	Cat 1	–	–	–	–
	Cat 2	–	35	++	R (24 hours)
Boiled:	Cat 1	–	45, 60	++++	D (7 days)
	Cat 2	30	65	++	R (2 days)
C (Hemolytic paracolon from fatal case)					
Unheated:	Cat 1	30	90	++	R (24 hours)
	Cat 2	–	–	–	–
	Cat 3	mucus	–	+	R (Few hours)
	Cat 4	85	35, 65	++	R (24 hours)
	Cat 5	7, 60	35, 40, 45, 50	+++	R (24 hours)
	Cat 6	6, 32, blood	20, 27	++++	D (18 hours)
Heated:	Cat 1	–	–	–	–
Boiled:	Cat 1	35	–	+	R (Few hours)
D (Nonhemolytic colon from fatal case)					
Unheated:	Cat 1	–	–	–	–
Heated:	Cat 1	–	–	–	–
	Cat 2	–	35	+	R (Few hours)
	Cat 3	–	5, 15, 25	++	R (18 hours)
Boiled:	Cat 1	45	–	+	R (Few hours)
	Cat 2	45, mucus	–	+	R 18 hours)
E (Hemolytic colon from infant with loose stools)					
Unheated:	Cat 1	5, mucus	30, 35	++	R (24 hours)
Boiled:	Cat 1	30, 75	80	+++	R (48 hours)
F (Nonhemolytic colon from normal infant in same nursery with Strain E)					
Unheated:	Cat 1	–	70	+	R (18 hours)
Boiled:	Cat 1	75	70	++	R (18 hours)
G (Paracolon from infant with loose stools)					
Unheated:	Cat 1	30	–	+	R (Few hours)
H (Paracolon from infant with loose stools)					
Unheated:	Cat 1	25	45, 55	++	R (24 hours)

three kittens remained normal, but the old cat developed diarrhea after forty-eight hours, and this diarrhea persisted for several days. A culture of Strain B (hemolytic colon) was fed to an older cat, and it had diarrhea for one day, commencing forty-eight hours after injection. Strain C (paracolon) was fed to one kitten and two older cats but no diarrhea was produced.

Man.—A human volunteer, 45 years of age, swallowed live cultures of Strains A and C growing in milk and no symptoms were produced.

Guinea Pig.—One-day-old guinea pigs were fed cultures of Strain A without any effect.

Mice.—Mice were fed cultures of Strain A without producing any symptoms.

EXPERIMENTS ON TOXIN PRODUCED BY GROWING COLON AND PARACOLON ORGANISMS IN 10 PER CENT CARBON DIOXIDE AND 90 PER CENT AIR

Strains of colon and paracolon isolated from an infant's tissues at autopsy and from the stools of sick infants were grown in 0.3 per cent semisolid agar similar to that used for producing staphylococcus enterotoxin.[3] They were grown for forty-eight hours at 37° C. in an atmosphere of 10 per cent carbon dioxide and 90 per cent air. The agar was then centrifuged and the supernatant fluid passed through a Berkefeld filter. This is known as unheated toxin. Another portion was heated to 56° C. for thirty minutes and a third portion was boiled for thirty minutes.

Injection of Toxin Into Cats.—Cats of different ages were given intra-abdominal injections of 2 c.c. of (1) unheated toxin, (2) heated toxin, and (3) boiled toxin of colon and paracolon organisms. All the strains tested produced symptoms. Some cats were very susceptible, while others were quite refractory. The following symptoms were noted. From five to thirty minutes after injection susceptible cats generally developed loose stools which rapidly became diarrheic, and in acute cases blood and mucus appeared in the stool as soon as twenty minutes after injection. From thirty to sixty minutes after injection, the cats vomited and this recurred several times during the next hour. Some of the cats repeatedly stretched themselves with arched backs until vomiting occurred. Many of the cats had chills.

In Table III are recorded the symptoms which occurred on injecting different toxins into cats, showing the relative pathogenicity of the toxins and the termination in each case.

Strains A, B, and C (hemolytic colon and paracolon) were quite toxic for the cats. With each strain the unheated toxin produced death in some cats, although other cats injected with the same material were quite refractory.

Strain D (nonhemolytic colon) toxin was not as toxic as the other strains, but two cats vomited when injected with the heated toxin.

Strains E, F, G, and H were isolated from infants in Hospital A. These infants had loose stools but were not very sick.

Strain E (hemolytic colon from an infant with loose stools) was more toxic than Strain F (nonhemolytic colon from a normal infant). Strains G and H were two paracolon organisms isolated from infants with loose stools in the same nursery. These strains were not very toxic, although vomiting was produced in one cat by the unheated toxin of Strain H.

TABLE IV

INJECTION OF TOXINS OF STRAIN A (HEMOLYTIC COLON) AND STRAIN C (PARACOLON), PRODUCED BY GROWING ORGANISMS IN 10 PER CENT CARBON DIOXIDE IN AIR, INTO KITTENS OF THE SAME LITTER

INJECTION			SYMPTOMS (MINUTES ELAPSING BEFORE SYMPTOMS APPEARED)		RECOVERY OR DEATH
KITTEN	DATE	STRAIN	DIARRHEA	VOMITING	
1	April 16	A unheated	70	40, 55	R
	May 6	C unheated	15, 45	-	R
2	April 16	A boiled	-	-	-
	May 6	C unheated	6, 32	20, 27	D
3	April 16	C unheated	7, 60	35, 40, 45, 50	R
	May 6	A unheated	-	Chills	R

In Table IV is recorded the result of injections of hemolytic colon and paracolon toxins into three kittens of the same litter, 1 month of age. One of the kittens injected with the paracolon toxin, unheated, died in less than eighteen hours. The hemolytic colon toxin appeared to be somewhat less toxic for these kittens than the paracolon toxin.

TABLE V

EFFECT OF REPEATED INJECTIONS AT WEEKLY INTERVALS OF STRAIN A (HEMOLYTIC COLON) TOXIN, PRODUCED BY GROWING ORGANISMS IN 10 PER CENT CARBON DIOXIDE IN AIR, INTO THE SAME CAT

NUMBER OF INJECTION	MATERIAL INJECTED	SEVERITY OF SYMPTOMS WITH VOMITING
First	Strain A boiled	+++
Second	Strain A unheated with Strain A rabbit serum	++
Third	Strain A unheated	++
Fourth	Strain A unheated	++
Fifth	Strain A unheated with Strain A rabbit serum	++ (Anaphylactic shock)
Sixth	Strain A unheated	++
Seventh	Strain A unheated	++
Eighth	Strain A unheated	+ (No vomiting)

The cat in Table V was injected weekly for eight weeks with Strain A. Rabbit serum mixed with the toxin was given on two occasions. This serum was from a rabbit which had received Strain A toxin, unheated, given intravenously three times weekly for six weeks in increasing doses. Two cubic centimeters of toxin were mixed with 2 c.c. of serum and given intra-abdominally. From these experiments it appears that the

cat does not become immunized by repeated injections of the same toxin for as many as eight injections at weekly intervals. Serum from a rabbit injected with toxin did not have any effect in preventing vomiting in the cat.

Injection of Colon Toxins, Grown in 10 Per Cent Carbon Dioxide and 90 Per Cent Air, Into Other Animals.—

Mice: Mice were injected intra-abdominally with 1 c.c. of the boiled and unheated toxins of Strains A, B, C, and D (two mice with each strain). One mouse injected with Strain D boiled toxin died in thirteen days and one injected with the unheated toxin, in four days. One mouse injected with Strain A unheated toxin died in seven days.

Rat: Strain A unheated toxin, 1.5 c.c., was injected intra-abdominally into a rat with no reaction.

Guinea Pig: A guinea pig, 2 days old, was given 1 c.c. intraabdominally of Strain A unheated toxin. No reaction.

Rabbit: A rabbit was injected with 2 c.c. intravenously of the unheated toxin of Strain A. No reaction.

Monkey: Four monkeys were given 2 c.c. intravenously of the boiled toxins of Strains A, B, C, and D and one hour later 2 c.c. of the unheated toxin of the same strains. The monkey injected with the Strain D toxin vomited one hour after the last injection. The other monkeys remained normal.

TABLE VI

INTRA-ABDOMINAL INJECTIONS INTO CATS OF HEMOLYTIC COLON AND PARACOLON TOXINS PRODUCED BY GROWING THE ORGANISMS IN 30 PER CENT CARBON DIOXIDE AND 70 PER CENT OXYGEN

STRAIN	SYMPTOMS (MINUTES ELAPSING BEFORE ONSET OF SYMPTOMS		PATHOGENICITY	RECOVERY OR DEATH
	DIARRHEA	VOMITING		
Strain A (Hemolytic colon from fatal case)				
Unheated: Cat 1	35, 120	-	++++	D (10 days)
Cat 2	10, 23	22, 30, 37, 43	+++	R (24 hours)
Boiled: Cat 1	-	28, 33, 35	++++	D (8 hours)
Cat 2	3	35, 40, 48	+++	R (24 hours)
Strain C (Paracolon from a fatal case)				
Unheated: Cat 1	32, 130	37,	++++	D (4 days)
Boiled: Cat 1	17	40, 48, 53	+++	R (24 hours)

In Table VI the toxins injected into cats were produced by growing the organisms in 30 per cent carbon dioxide and 70 per cent oxygen. One cat died in eight hours after being given 2 c.c. of hemolytic colon toxin which had been boiled for thirty minutes, while another cat died in ten days after injection with unheated hemolytic colon toxin. One cat injected with unheated toxin from paracolon died after four days.

DISCUSSION

The outbreaks described varied markedly in their virulence. In Hospital C there were no deaths, while in Hospital D there were twelve deaths. In each instance the nursing techniques were very faulty. In two hospitals the diapers were rinsed in a sink in the nursery and the complementary feedings for the infants were warmed in the same sink. Invariably the feedings were made up in quart stock bottles and poured later into the feeding bottles at the feeding periods.

Hemolytic colon organisms were present more frequently among sick infants than in normal infants in the same nursery. In the epidemic where there was a high case fatality, paracolon organisms were also present in large numbers in the feces of the infants. Michelson and Dulaney in 1935 stated that in their investigations they had substantial proof that *E. coli* mutabile was the cause of an outbreak of infantile diarrhea, but these organisms may have been secondary to an unrecognized organism as the primary cause. The organisms which they described fermented saccharose, while the paracolon organism isolated from the fatal case in Hospital D did not ferment this sugar.

These colon and paracolon organisms produced hemolysis of sheep blood cells when growing on blood agar plates, but their toxins made by growing the organisms in partial carbon dioxide tension in semisolid agar did not produce any hemolytic titer for rabbit or sheep blood cells.

Strains of hemolytic colon and paracolon from the fatal case were grown in milk and fed to cats. Two older cats fed with the hemolytic colon organisms developed diarrhea but in the kittens no diarrhea was produced. These strains did not produce any symptoms when fed to mice, guinea pigs, or man.

The two hemolytic colon and paracolon toxins from the fatal case were very toxic for cats, while the nonhemolytic colon toxin was less toxic. In a milder epidemic in another hospital the hemolytic colon toxin from a mild case was more toxic than the nonhemolytic colon toxin from a normal infant. These toxins were atoxic for rats, guinea pigs, or monkeys. They were more toxic for mice. The toxins grown in 30 per cent carbon dioxide with 70 per cent oxygen appeared to be somewhat more toxic for cats than those grown in 10 per cent carbon dioxide and 90 per cent air.

In Hospital D, where there were twelve deaths, both hemolytic colon and paracolon organisms were present in most of the sick infants. It is possible that either the paracolon or hemolytic colon or both organisms were the cause of the epidemic.

From the epidemiologic and bacteriologic investigations carried out on these epidemics it would appear that hemolytic colon and paracolon organisms and their toxins are intimately associated with epidemic diarrhea of the newborn infant.

SUMMARY

1. Hemolytic colon organisms show a much greater incidence in infants with epidemic diarrhea than in well infants in the same nursery.

2. These organisms, grown in milk and fed to cats, occasionally produce diarrhea.

3. Colon and paracolon organisms grown under partial carbon dioxide tension produce toxins. These toxins can be demonstrated by intraperitoneal injections into cats which produces vomiting and diarrhea. Death occurs with the more toxic strains. Boiled toxins also produce symptoms. There is a wide variation in the susceptibility of cats to these toxins, and some cats are refractory. Susceptible cats do not appear to develop an immunity from at least eight injections of the same toxin given at weekly intervals.

4. The colon toxins do not produce any hemolytic titer for rabbit or sheep blood cells.

5. In the epidemics investigated the most toxic strains of hemolytic colon and paracolon producing death in cats were isolated from a fatal case of epidemic diarrhea of the newborn infant. Toxins from a hemolytic colon organism isolated from an infant with loose stools in a mild epidemic produced milder symptoms. Nonhemolytic colon toxin from a fatal case produced milder symptoms than hemolytic colon or paracolon toxins from the same case.

6. Close association between the complementary feedings and the bathing and changing operations of the infants is a potent source in the spread of this infection.

My sincere thanks are due to A. L. MacNabb, Director of Ontario Provincial Laboratories, and to all others associated with me in this investigation, for valuable assistance.

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THE EFFECT OF SULFATHIAZOLE IN THE TREATMENT OF DYSENTERY IN CHILDREN

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AN INVESTIGATION of the effectiveness of sulfathiazole in the treatment of infectious diarrhea was begun in the Children's Division of the Cook County Hospital during the summer months of 1940. Forty-six cases were included in the study. In the preceding summer sulfanilamide was used for the treatment of similar cases but yielded unsatisfactory results. Reports of other observers who used sulfanilamide for this disease are inconclusive.[1-3]

With the introduction of sulfathiazole, a number of workers began investigating the value of this chemotherapeutic agent in the treatment of diarrhea. In 1939 Lawrence[4] reported in vitro studies in which sulfathiazole was found to be the most effective of the sulfonamide drugs against the colon-typhoid dysentery organisms. Below sulfathiazole in effectiveness were sulfapyridine, sulfaphenylthiazole, and sulfanilamide, in that order. Cooper and Keller,[5] comparing the effectiveness of sulfathiazole, sulfapyridine, sulfamethylthiazole, and sulfanilamide, in protecting mice against fatal doses of *Shigella paradysenteriae* Flexner, found sulfathiazole to be the most effective and sulfanilamide to be the least effective.

Libby's[6] work revealed that, in vitro, sulfathiazole is more effective against the Flexner dysentery bacillus than were the other sulfanilamide compounds. Taylor[7] concluded that sulfathiazole is effective in the treatment of children with parenteral diarrhea or bacillary dysentery, particularly in the latter. Good results in the sulfathiazole treatment of infectious diarrhea have been reported by other workers;[8-10] some of these studies, however, were inadequately controlled.

Since completing this study, Cooper and his associates[11] have published their results from a similar study, concluding that sulfathiazole is of greater therapeutic value in those patients whose stool cultures are positive for dysentery organisms than in the treatment of patients whose stools are negative for these pathogens. This conclusion agrees in the main with our findings.

The children included in the present study entered the Cook County Children's Hospital because of frequent, watery stools containing blood and mucus. They were, in general, somewhat less severely ill than those

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admitted in previous years with similar complaints. The number of patients with diarrhea entering the hospital during the early part of the summer was smaller than in former years, and patients continued to enter the hospital later into the autumn months than was to be expected from our previous experience. It is of epidemiologic interest that during this same period the incidence of anterior poliomyelitis in the Chicago vicinity also remained at a higher level during the late autumn months than had been the case in previous years.

METHODS

The patients were divided into two groups: namely, Group A, which was treated with sulfathiazole; and Group B, the control group, not treated with the drug. Strict adherence to an alternating schedule in the selection of the control cases did not prove to be advisable, since in some of the extremely sick patients it was felt that to withhold the drug, with its possible therapeutic advantages, was unfair to these patients. However, patients in each group were sufficiently widespread over the entire period to provide an adequate basis for comparison.

Sulfathiazole was started from two to four days after the patient's admission to the hospital and continued until the child was clinically well, the stools normal in number, color, and consistency, and until three consecutive negative stool cultures had been obtained at intervals of at least one week. The average dosage of the drug was 1.5 gr. per pound of body weight per day, given in six equal doses at four-hour intervals.

Nonspecific, supportive therapeutic measures were employed on all patients, as indicated by their clinical condition. These measures included the administration of parenteral fluids (2½ per cent dextrose in physiologic saline solution or Hartmann's solution), blood transfusions, and sedatives.

All patients with severe diarrhea were placed on an initial starvation routine for twenty-four hours. During this period those able to take liquids by mouth were given weak tea in small amounts and at frequent intervals; those who were comatose or were vomiting were given nothing by mouth.

As the clinical condition and type of stool improved, the patient was given Diet A, which consisted of cultured skimmed lactic acid milk, or Enzylac, or a combination of these. The diet was given in relatively small amounts every four hours. With further improvement of the clinical condition of the patient and lessened frequency of the stools, Diet B was added. This consisted of jello, cottage cheese, fat-free broth, soda crackers, white toast, and strained orange juice. Later the constituents of Diet C were added. These additions included custard, mashed ripe bananas, freshly grated raw apple, and cereal.

On admission, blood was obtained from each patient for a complete blood count, blood culture, and determinations of the CO_2 combining

TABLE I

COMPARATIVE STUDY OF DURATION OF DIARRHEA IN SULFATHIAZOLE-TREATED AND CONTROL PATIENTS

BACTERIOLOGY	GROUP	AVERAGE DAYS OF DIARRHEA IN HOSPITAL	BEFORE SULFATHIAZOLE	AFTER SULFATHIAZOLE	RECTIFIED NUMBER OF DAYS
Positive	A_2 (Treated)	5.6	2.7	2.9	2.9
	B_2 (Control)	11.5	-	-	8.8
Negative	A_1 (Treated)	6.3	1.6	4.7	4.7
	B_1 (Control)	6.3	-	-	4.7

TABLE II

EFFECT OF SULFATHIAZOLE IN THE TREATMENT OF DYSENTERY

GROUP A_1 (CULTURES NEGATIVE; TREATED WITH SULFATHIAZOLE)

CASE	DEGREE OF SEVERITY			DURATION OF DIARRHEA (DAYS)				LAG*
	SEVERE	MOD.	MILD	BEFORE ADM.	AFTER ADM.	TOTAL	AFTER SULFATHIAZOLE	
6		x		4	4	8	1	3
10	x			1	3	4	2	1
15		x		?	7	?	4	3
19			x	2	4	6	3	1
26	x			4	5	9	4	1
33		x		30	16	46	15	1
36		x		8	4	12	3	1
43		x		7	12	19	10	2
46		x		3	2	5	1	1
	Total			*Average*				
9	2	6	1	7.4	6.3	13.7	4.7	1.6

Average number of stools on day admitted to hospital	7
Average duration of fever (days)	3
Average duration of sulfathiazole treatment (days)	17.5
Leucopenia	1
Hematuria	4

*Lag: Days of nonspecific therapy before sulfathiazole was begun.

TABLE III

EFFECT OF SULFATHIAZOLE IN THE TREATMENT OF DYSENTERY

GROUP A_2 (CULTURES POSITIVE; TREATED WITH SULFATHIAZOLE)

CASE	DEGREE OF SEVERITY			DURATION OF DIARRHEA (DAYS)				LAG*
	SEVERE	MOD.	MILD	BEFORE ADM.	AFTER ADM.	TOTAL	AFTER SULFATHIAZOLE	
2		x		2	4	6	3	1
11		x		5	14	19	2	12
16		x		3	7	10	4	3
17		x		29	7	36	5	2
23	x			1	3	4	2	1
24		x		1	3	4	2	1
42		x		4	3	7	2	1
30		x		4	4	8	3	1
	Total			*Average*				
	1	7	0	6.1	5.6	11.7	2.9	2.7

Average duration of fever (days)	3.7
Average number of stools on day admitted to hospital	5.3
Average duration of sulfathiazole treatment (days)	19.7
Toxic leucopenia	-0-
Hematuria	1

*Lag: Days of nonspecific therapy before sulfathiazole was begun.

power, total protein, albumin, globulin, chlorides, and cevitamic acid content.

Urine and stool specimens were obtained on admission for culture, and cultures of the stools were repeated until those patients with positive cultures showed three consecutive negative cultures. Those whose initial stool cultures were negative were repeatedly cultured while in the hospital.

Determinations of the sulfathiazole concentration in the blood were done at frequent intervals. Duration of hospital stay was prolonged in many instances for the purposes of study.

Although they were clinically improved and their stools normal long before the time of discharge, the patients with positive stool cultures were held until three negative cultures were obtained. Those with initial negative cultures also remained in the hospital until their study was completed.

RESULTS

There were no deaths in the entire series.

For the purpose of analysis, Group A (treated with sulfathiazole) was subdivided into Group A_1, consisting of nine patients whose stool cultures were negative for specific pathogenic organisms, and Group A_2, consisting of eight patients whose stool cultures were positive.

Group B (controls, not treated with sulfathiazole) was subdivided into Group B_1, consisting of sixteen patients with stool cultures negative for specific organisms, and Group B_2, consisting of thirteen patients with positive stool cultures.

The duration of the diarrhea after starting sulfathiazole was taken as the criterion of the effectiveness of the drug. Table I shows a comparison of the duration of diarrhea in the sulfathiazole-treated and the control patients.

The analysis of the effectiveness of sulfathiazole, based upon the duration of diarrhea in the sulfathiazole-treated patients as compared with the control patients, is shown in Tables II, III, IV, and V.

Sulfathiazole was continued during the entire period of hospitalization, except in five children in whom hematuria occurred and in one with a leucopenic reaction. The drug was tolerated very well by most of the children, with very little nausea or vomiting. The average blood sulfathiazole level was 4.14 mg. per 100 c.c. in patients in Group A_1, and 2.87 mg. in patients in Group A_2.

In the five children in whom hematuria occurred, it was mild, lasting one to three days, resulting in complete recovery after the drug was discontinued. In only one instance were significant blood changes noted. This child showed a 30 per cent reduction in the total white count and a 60 per cent reduction in polymorphonuclear leucocytes, with a complete recovery after stoppage of the drug. Fever was present for an average of three to four days in each group.

The patients in Group A_1 (cultures negative, treated with sulfathiazole) had diarrhea lasting an average of 4.7 days after sulfathiazole

TABLE IV

EFFECT OF SULFATHIAZOLE IN THE TREATMENT OF DYSENTERY

GROUP B_1 (CULTURES NEGATIVE; CONTROL PATIENTS)

CASE	DEGREE OF SEVERITY			DURATION OF DIARRHEA (DAYS)		
	SEVERE	MOD.	MILD	BEFORE ADM.	AFTER ADM.	TOTAL
4		x		21	3	24
8	x			3	6	9
9		x		5	10	15
12		x		14	4	18
13			x	14	4	18
14		x		1	6	7
18			x	21	0	21
20		x		1	5	6
21			x	3½	5	8½
22		x		7	7	14
27		x		3½	11	14½
34			x	1	10	11
37			x	?	11	?
38			x	18	0	18
44			x	6	4	10
45		x		3	15	18
	Total			*Average*		
16	1	8	7	8.1	6.3	14.4
Average number of stools on day admitted to hospital						2.8
Average duration of fever (days)						3.5

TABLE V

EFFECT OF SULFATHIAZOLE IN THE TREATMENT OF DYSENTERY

GROUP B_2 (CULTURES POSITIVE; CONTROL PATIENTS)

CASE	DEGREE OF SEVERITY			DURATION OF DIARRHEA (DAYS)		
	SEVERE	MOD.	MILD	BEFORE ADM.	AFTER ADM.	TOTAL
40		x		1	6	7
41			x	?	27	27?
39		x		1	4	5
35		x		4	7	11
32	x			1	14	15
31		x		1½	7	8½
29		x		1	6	7
28			x	4	1	5
25	x			5	14	19
7	x			1	16	17
5	x			1	17	18
3			x	7	7	14
1		x		7	24	31
	Total			*Average*		
13	4	6	3	2.8	11.5	14.3
Average number of stools on day admitted to hospital						2.4
Average duration of fever (days)						3.3

was started. In this group sulfathiazole was started an average of 1.6 days after admission to the hospital. This period is denoted as the "lag" period. The patients in Group B_1 (cultures negative, control patients) had diarrhea lasting 6.3 days after admission to the hospital. In order to rectify the factor of general nonspecific therapy in both

groups, we subtract 1.6 days of "lag" from 6.3 days, which leaves 4.7 days, a more equitable figure, and one which is comparable to and identical with the duration of the diarrhea in patients in Group A_1 after sulfathiazole was started (Tables I, II, IV).

It is evident that in these two culturally negative groups of patients there is no difference in the duration of the diarrhea after entering the hospital. As seen in the tables, however, there was a greater number (44 per cent) of mild cases in the control patients than in the sulfathiazole-treated patients, in which group only 11 per cent were mild. This inequality in sampling probably did not influence the statistical result since similar results have been reported by other observers.

The patients in Group A_2 (cultures positive and treated with sulfathiazole) had diarrhea lasting an average of 5.6 days after entering the hospital. Since sulfathiazole was started in this group after 2.7 days (average) in the hospital, the duration of diarrhea after institution of drug therapy was 2.9 days (average). The patients in Group B_2 (cultures positive, control patients without sulfathiazole) had a diarrhea lasting an average of 11.5 days after admission to the hospital (Tables I, III, V).

In the patients in Group A_2 sulfathiazole was started following an average "lag" period of 2.7 days after admission to the hospital. During this lag period, the patients in Group A_2 as well as in Group B_2 received nonspecific general therapy. If we subtract the lag of 2.7 (the period used for primary stool culture) from 11.5, we get 8.8 days as a comparable average duration of diarrhea in patients in Group B_2. This is a more equitable figure to be compared with 2.9 days, the average duration of diarrhea in the positive culture, sulfathiazole-treated patients in Group A_2.

The duration of the diarrhea was shorter in treated patients from whose stools *Bacillus dysentericus* or Salmonella organisms were obtained than from those in whom these organisms were not found. The average duration of diarrhea was 2.9 days in the former and 4.7 days in the latter.

TABLE VI

STOOL BACTERIOLOGY

GROUP	NUMBER OF CASES	ORGANISM NOT IDENTIFIED	BACILLUS DYSENTERICUS					SALMONELLA GROUP		
			UNCLASSIFIED	HISS	FLEXNER	STRONG	SONNE	UNCLASSIFIED	AERTRYCKE	ENTERITIDIS
A_1	9	9	0	0	0	0	0	0	0	0
B_1	16	16	0	0	0	0	0	0	0	0
A_2	8	0	0	1	4	1	1	0	0	1
B_2	13	0	3	5	1	0	1	1	2	0

Table VI shows the results of the bacteriologic studies of the stools. There were twenty-five patients from whose stools no pathogenic organisms could be identified and twenty-one patients from whose stools pathogens were recovered. In the latter group, the predominant pathogenic organisms were of the *B. dysentericus* group; less frequently those of the Salmonella group.

Analysis of blood chemistry studies revealed little of significance, except for consistently low values for the cevitamic acid content, average 0.32 mg. per 100 c.c., and low values for the CO_2 combining power in those most severely ill patients with clinical signs of dehydration and acidosis. The blood studies revealed few significant changes in the total protein, serum albumin and globulin, and chloride content.

SUMMARY AND CONCLUSIONS

1. Patients with clinical dysentery, and from whose stools positive cultures of *B. dysentericus* and Salmonella were obtained, responded to sulfathiazole better than a group clinically identical but with negative stool cultures. The ratio of duration of disease after treatment was started is 2.9 to 4.7 days.

2. Patients with clinical dysentery and positive stool cultures, treated with sulfathiazole, had a shorter duration of their diarrhea after sulfathiazole was started than did patients with like clinical and bacteriologic findings treated identically but without sulfathiazole. The ratio of days of diarrhea after sulfathiazole was started was 2.9 to 8.8. (The figure 8.8 was obtained by subtracting 2.7, the hospital day on which sulfathiazole was first given to patients in Group A_2, from 11.5, the days of duration of diarrhea after the patients in Group B_2 entered the hospital.) This rectifies and equalizes the factor of days of nonspecific treatment in the two groups designated as the "lag" period.

3. In the group of children studied, sulfathiazole appeared to have definite value in the treatment of those whose stool cultures were positive for dysentery or Salmonella organisms. In the groups in which these organisms were not identified, no statistically significant effect is demonstrated.

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VITAMIN K IN HEMORRHAGIC DISEASE OF THE NEWBORN INFANT

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IN A previous report[1] it was shown that hemorrhagic disease of the newborn infant was associated with low plasma prothrombin and could be cured by the administration of synthetic vitamin K by mouth or intravenously. Also it was found that a number of newborn infants had a low prothrombin at birth, and this could be prevented largely by giving synthetic vitamin K by mouth to the mothers in daily doses for a period preceding delivery. Because of the difficulty in estimating the actual time of probable onset of labor and to be of practical value to the practicing physician, an attempt was made to see how near delivery the vitamin K could be given and still be effective. Also, observations were made on the treatment of hemorrhagic disease by the intramuscular injection of vitamin K.

Five capsules, each containing 1 mg. of synthetic vitamin K (2 methyl 1-4 naphthoquinone)* in oil were given by mouth to mothers after the onset of labor immediately on admission to the hospital. Approximately alternate cases received this, and the others were used as controls. Cord bloods were obtained at delivery on all babies. Prothrombin time on the cord bloods was estimated by the method of Quick which consists of recalcifying oxalated plasma to which a thromboplastin solution has been added and measuring the time for clot formation.

In addition, prothrombin estimations were carried out daily for ten days on all the babies by a micromethod, using capillary blood obtained from the heel. The method consists in mixing 0.09 c.c. of blood from a heel puncture with 0.01 c.c. of molar solution of sodium oxalate. This is obtained in a 0.2 c.c. pipette graduated in 0.01 c.c. The oxalated blood is placed in a test tube 8 to 10 mm. in diameter. Thromboplastin solution (0.1 c.c.) prepared according to Quick's method is added to the oxalated blood and then it is recalcified with 0.1 c.c. of calcium chloride containing 0.247 Gm. per 100 c.c. With a platinum wire loop, the time taken for clotting to occur, following the complete addition of the calcium, is measured with a stop watch. With this method in normal persons fifteen to twenty seconds are the limits of clotting. We have compared samples from the same individuals using this method and the method of Quick and find that the two methods correlate.

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*Kindly supplied by E. R. Squibb & Co.

TABLE I

INTERVAL OF PROTHROMBIN TIME IN SECONDS FOR CORD BLOOD (PERCENTAGE OF CASES)

		0 TO 30 SEC. (%)	31 TO 60 SEC. (%)	61 TO 90 SEC. (%)	91 TO 100 SEC. (%)	121+ SEC. (%)
Controls*	88 cases	7	57	17	5	14
Vitamin K†	80 cases all cases	2.5	72.5	20	2.5	2.5
Vitamin K‡	60 cases	12.5	73.5	14		

*No vitamin K.

†Mothers received 5 Gm. of vitamin K (2 methyl 1-4 naphthoquinone) by mouth on admission to hospital. In all cases labor had commenced.

‡Mothers receiving vitamin K over four hours before delivery. Quick's method used.

TABLE II

DAILY PROTHROMBIN TESTS UP TO TENTH DAY OF AGE (MICROMETHOD)

	NUMBER OF CASES	ALL TESTS BELOW 25 SEC. (%)	ANY TEST ABOVE 25 SEC. (%)
No vitamin K	140	43.5	56.5
Vitamin K*	43	98	2

*Five milligrams of vitamin K administered to mother by mouth over four hours before delivery.

The prothrombin times of cord blood (Table I) for the control cases fall into the same spread as previously reported; viz., that though a number were within limits where bleeding was not likely, 14 per cent, however, were in the level (i.e., greater than 120 seconds) where hemorrhagic disease occurred. For all the infants whose mothers were given vitamin K on arrival at the hospital after the onset of labor, 2.5 per cent were markedly prolonged and 2.5 per cent were somewhat prolonged in prothrombin time. If the infants whose mothers received the vitamin K less than four hours before delivery are eliminated, then none are in the prolonged group. Thus we have shown that 5 mg. of thyloquinone in oil by mouth, given after the onset of labor but more than four hours before delivery, will protect the infant from hypoprothrombinemia. It is necessary to be sure that the mother does not vomit the vitamin K.

Micro-estimations of prothrombin on capillary blood were done on these babies daily. By this method where the mother received vitamin K more than four hours, most were less than twenty seconds or within normal limits (Fig. 1). If one takes twenty-five seconds (Table II), which is much less than the times observed in any case with bleeding, then only one estimation in forty-three infants was over this figure, whereas 79 of 140 control infants had one or more estimations over twenty-five seconds. Thus we were able to show that five capsules each containing 1 mg. of 2 methyl 1-4 naphthoquinone (thyloquinone) in oil given to the mother lowers the prothrombin time of cord blood and also the prothrombin time of the blood during the first ten days of life, which is the period when hemorrhage is most likely to occur.

As previously reported, vitamin K administered intravenously and by mouth has proved effective in lowering the prothrombin time in cases of hemorrhagic disease. Subsequently vitamin K-like synthetic compound has been given intramuscularly in the treatment of hemorrhagic disease of the newborn infant. The compounds used by us so far are:

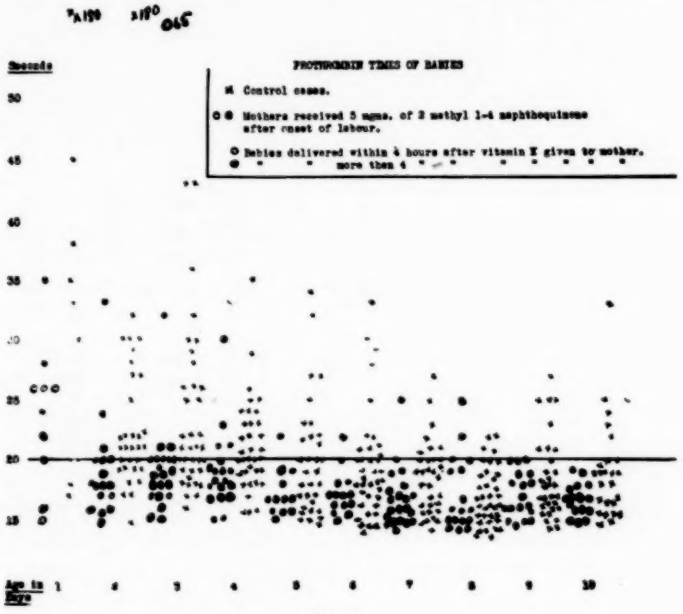

Fig. 1.

(a) the same solution that was used intravenously. This synthetic vitamin K (2 methyl 1-4 naphthoquinone), a powder, 10 mg. of which was enclosed in a glass capsule. The contents of this were dissolved in 100 c.c. of normal saline which was then boiled ten minutes for purposes of sterilization. This material should be kept out of the direct light and stored, if possible, in the refrigerator after it has been made up. (b) A solution of thyloquinone (2 methyl 1-4 naphthoquinone) in corn oil, 2 mg. per cubic centimeter. (c) An amino quinone compound* (4 amino 2 methyl 1 naphthol) which is water soluble and may be given intravenously or intramuscularly (Table III). Three cases were treated with the saline solution containing 1 mg. in 10 c.c.; five were treated with the thyloquinone in oil and one with the amino compound. The prothrombin of the blood was lowered in all. The second estimation was made in from four to twelve hours. Thus it is shown that vitamin K-like compounds given intramuscularly are effective in lowering the prothrombin time and controlling the bleeding in hemorrhagic disease of the newborn infant.

*Kindly supplied by Parke Davis & Co.

TABLE III

RESULTS OF TREATMENT OF HEMORRHAGIC DISEASE OF THE NEWBORN INFANT WITH VITAMIN K INTRAMUSCULARLY

PATIENT	AMOUNT VITAMIN K (MG.)	PROTHROMBIN TIME (SEC.)		RESULT
		ADMISSION	AFTER TREATMENT	
1	2*	60	34	Bleeding per rectum—stopped
2	2*	120	54	Bleeding stopped
3	2*	660	50	Bleeding stopped
4	2†	115	45	Bleeding stopped
5	2†	120	27	Died, massive intracranial hemorrhage
6	2†	92	50	Bleeding stopped
7	2†	150	40	Bleeding stopped
8	2†	70	26	Bleeding stopped
9	2†	240	48	Bleeding stopped
10	2‡	?	30	Bleeding stopped

*Saline solution of vitamin K same as used intravenously. (Kindly supplied by E. R. Squibb & Co.)

†Solution of 2 mg. 2 methyl 1-4 naphthoquinone in 1 c.c. corn oil.

‡4 amino 2 methyl 1 naphthol in aqueous solution, 1 mg. per cubic centimeter.

In the treatment of hemorrhagic disease then, vitamin K intravenously or intramuscularly is effective. If given early, before much blood is lost, it will be adequate but after the hemoglobin is materially lowered, transfusion is necessary as well. In our experience vitamin K has done away with the necessity of second transfusions. To recapitulate then, given a case of hemorrhagic disease of the newborn, check hemoglobin; if low, give vitamin K and transfuse. If hemoglobin is normal, give vitamin K intravenously or intramuscularly.

TABLE IV

DAILY PROTHROMBIN TESTS UP TO TENTH DAY OF AGE (MICROMETHOD)

MONTH	NUMBER OF CASES	TESTS BELOW 25 SEC. (%)	TESTS ABOVE 25 SEC. (%)
January	37	48.5	51.5
February	28	40	60
March	27	15	85
April	25	64	36
May	23	51	49

None of the mothers had received vitamin K by mouth.

An interesting fact comes from examining the prothrombin times of the control infants by monthly intervals from January to May. During February and March (Table IV), which is the seasonal incidence of hemorrhagic disease of the newborn, a very high percentage showed definitely marked prolonged prothrombin times. Of these infants in March, there were three who developed definite hemorrhage. In one infant no treatment was given, and the prothrombin time returned to normal. The hemorrhage had occurred in the twenty-four-hour interval between making two daily tests, and when it was found

with the second test that the prothrombin time was decreased, vitamin K was not given. Obviously this baby had synthesized its own vitamin K from its intestinal tract.

The diets of the mothers were checked to see if there was any relation to the lack of vitamin K in the diet and low prothrombin in the infant. The mothers were asked if their prepartum diet contained the following substances: whole grain cereals, whole wheat bread, leafy vegetables, meats, eggs, fruit, and milk. As a result of this survey, no relation was found between the regular ante-partum diet of the mother and the prothrombin content of the infant's blood.

SUMMARY

1. Thyloquinone (2 methyl 1-4 naphthoquinone) in oil given by mouth in 5 mg. doses to mothers after labor has commenced, at least more than four hours before delivery, will prevent extreme degrees of hypoprothrombinemia in the newborn infant at birth and during the first week or ten days of life. It will prevent hemorrhagic disease of the newborn infant.

2. Hypoprothrombinemia in untreated infants has a seasonal incidence, being much more frequent in February and March, which is the period that hemorrhagic disease is common.

3. One infant with hemorrhagic disease observed recovered spontaneously.

4. The diet of the mother bore no relation to the hypoprothrombinemia of the offspring.

5. Vitamin K-like compounds given intramuscularly are effective in lowering the prothrombin time.

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ASSESSING THE PHYSICAL CONDITION OF CHILDREN

I. Case Demonstration of Failing Growth and the Determination of "Par" by the Grid Method

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THE chief burden of assessing the physical condition of children has heretofore fallen on the task of appraising what is generally referred to as a child's nutrition. This, however, is but part of the larger problem of growth and development;[1] for the really crucial question which must be solved by those physicians who accept the responsibility for the care of child health is, in simplest terms, whether a given child is getting along as well as he should. Apart from disease this question is obviously answered the moment the physician can decide whether growth and development in a given child are operating satisfactorily, and, if not, in what respect as well as to what extent these processes manifest objectionable features.

Basically, the Grid technique of appraisal, as originally described,[2, 3] provides a systematic procedure which enables the physician to determine quantitative ratings on various attributes such as physique or body build, developmental level, and nutritional grade, among others, that enter simultaneously into a child's physical make-up. Since these attributes are almost inextricably mixed up in any one child, it is literally impossible by inspection or measurement to determine what part of the whole child may be ascribed to physique, what or how much of him may be ascribed to development, or, with physique and development both involved, how any of the remaining factors, such as age, have contributed to what is seen and measured. Yet it is precisely information on these points that is required in order to assess the child or to evaluate his growth and development and, finally, to explain what various deviations in physique, development, or physical progress may imply or actually signify.

By simply plotting data on height, weight, and age on a chart previously described[2, 3] and called a Grid,* it is possible to separate the individual effects of these different physical attributes and to assess each

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The material of the present series of papers, I, II, III, has been presented in part, illustrated by animated charts and by kodachrome motion picture and lantern slides, at the Scientific Exhibit of the American Medical Association, Cleveland, June 2 to 6, 1941, and at meetings of the Detroit Pediatric Society, Detroit, Mich., April 30, 1941; of the Milwaukee Pediatric Society, Milwaukee, Wis., June 11, 1941; of the New York Society of Orthodontists, New York City, Nov. 10 and 11, 1941; of the Committee on Growth and Development, University of Chicago, Nov. 25, 1941; of the Ohio State Medical Association, Columbus, April 29, 1942; of the American Academy of Pediatrics, Region III, Cleveland, May 14, 1942; and of the Kansas City Southwest Clinical Society, Kansas City, Mo., Oct. 8 and 9, 1942.

*The Grid for evaluating physical fitness is published by NEA Service, Inc., 1200 West Third Street, Cleveland, Ohio.

item by itself or, again, to combine one with another in order to reconstruct a graphic picture of physical progress. The resulting curves can be compared at a glance with the Grid standards marked out in the background of the chart. Moreover, any similarities, identities, and differences between the curves in question and the standards are automatically revealed as soon as the data are plotted and visualized. The entire procedure of assessment is objective; no computations are necessary; the steps are simple, and they lead to a systematic study of those pertinent features (physique, development, nutritional grade, etc.) which have been assembled into a single human being by the fundamental processes of growth and development. Lastly, one knows what kind of information can and cannot be extracted from the original height-weight data: either the "assembly" is doing well as far as growth and development are concerned or it is not doing so, in which case it needs to be investigated more comprehensively.

TWO MAJOR STEPS

In the Grid technique the assessment of physical condition has been reduced to only two major steps:

I. THE EVALUATION OF PHYSICAL STATUS, involving the study, measurement, and interpretation of:
   (a) Physique or body build.
   (b) Developmental level.
   (c) Nutritional grade.

II. THE EVALUATION OF PHYSICAL PROGRESS, or study of the relations between sequential physical states as defined by:
   (a) Channel course.
   (b) Auxodromic progress.

Step I is applied to each individual point that has been plotted from the original data on height and weight, whereas Step II concerns the resulting curves through those points. The mechanism of plotting the data in the two panels of a Grid has been described in previous publications[2, 3] and may therefore be assumed for the purposes of the present discussion. Reference may also be made to the same sources for the precise definitions of the various attributes, listed here as I (a), I (b), I (c), II (a), II (b). A more extended description with photographic illustrations of what physique, developmental level, etc. signify is now in press.[12] For the present it is sufficient to note merely that the assessment of physical condition by the Grid technique depends only on the systematic execution of the two foregoing steps and that an evaluation of progress can be constructed out of an evaluation of sequential physical states.

Two Guiding Principles

The analysis of each step and substep is based on two, and only two, guiding principles which may be simultaneously exercised simply by plotting routine values for height, weight, and age on a Grid. These two principles are:

1. Healthy progress prefers development along a channel of given body type on an age schedule or time table specific for the subject and with preservation of that subject's natural physique.

2. Each child should be considered his own standard of comparison.

Both principles serve to guide the physician not only in knowing what to look for but also how to interpret, use, and evaluate Grid ratings of physical condition.

The first principle establishes the rule for differentiating between satisfactory and unsatisfactory progress. It contains the simplest possible warning that enables the physician to detect and identify any child whose curves do not parallel the channel and auxodrome standards. The child, accordingly, is "screened" for further examination. The advantage of having unsatisfactory progress objectively identified—a matter which affects, incidentally, about one-third of all children—speaks for itself, and the challenge is usually rewarded by actually finding something in the child himself, his habits, or in his surroundings.

On the other hand, no equally extensive examination, especially in schools, will even be necessary for those children whose physical progress has thus been demonstrated to be satisfactory. They will require, if anything, no more than a search for minor physical defects, such as carious teeth, objectionable tonsils, or bad posture, for which suitable programs may be organized and carried out much more rapidly than otherwise, since these subjects have already passed the test of growth and development. Such a program will go far in avoiding the dull humdrum of examining too many well children only to find nothing. Thus the initial advantage of segregating children on the basis of satisfactory and unsatisfactory objective records of growth and development is by no means negligible in large scale work.

The second principle calls for treating each child as his own standard of comparison. This is also a fundamental tenet of the Grid method, as it must be in all endeavors to assess the physical condition of children. It has, to be sure, been employed from time to time as a practical rule in pediatrics to analyze and interpret the growth and development of young infants or even the emotional and psychologic problems of older children. It has permeated, though often vaguely, or in disguised form, into most discussions arising in child health and welfare work. But it has played no conspicuous role in these endeavors primarily because the traditional methods of handling height-weight data never permitted this basic principle to operate effectively even during the era when it became fashionable to stress the importance of "individual variations" and to denounce results drawn from "mass" rather than from "longitudinal" measurements on children.

Comparing Johnny with Jimmy rarely brings out anything valuable to either. What is really wanted is to know whether Johnny in his own right or Jimmy in his *is up to par with respect to himself*. This, in fact, is the acid test by which any method purporting to gauge the physical condition of children must be judged.

The Determination of Par

A child's par may be determined for each of the three components that make up physical status. What is still more important is that one may also determine whether a child is keeping up with par by plotting his height, weight, and age on a Grid. In fact, height, weight, and age are thereby actually translated from pounds and inches into units of body build, development, nutritional grade, physical status, etc., which themselves, as distinct from weights and heights, have direct meaning in the problem of assessing physical condition.

An interesting and simple analogy is worth mentioning. Heights and weights, in a very real sense, are like the letters of an alphabet. By themselves they mean nothing. If they are jumbled, they may even give misinformation. But, when once they are placed in an orderly array, in known combinations, and according to the rules of a language, they convey meanings to all who understand that language. Certain words, for example, contain the same letters but have different meanings (act, cat). Other words may have different spellings but sound alike (bare, bear). Quite similarly, figures representing heights and weights express almost nothing and mean painfully little until they are actually resolved into the attributes of physical condition outlined under Steps I and II. This can be convincingly demonstrated in the case of any child that might be chosen for study or investigation.

Take the case of T. B. in Table I as an illustration. What do these figures convey to even the experienced eye that surveys them in tabular form? What specifically do they tell us about body build? What about development, or about nutritional grade and physical status? Is the boy advanced or retarded? Above all, is he keeping to his schedule and does he show satisfactory progress or not? Not until these questions are answered shall one be able to assess him.

TABLE I

HEIGHTS AND WEIGHTS OF T. B.*

AGE (YR.)	WEIGHT (LB.)	HEIGHT (IN.)
7.00	48	46¼
7.60	51¼	47¼
8.00	54¼	48¼
9.50	62¼	51
10.75	67¼	52½
11.25	70¾	54½
12.25	76½	56
12.50	77	56¾

*From mere inspection of these figures the reader should attempt to reconstruct a mental image of what this boy looked like as regards body type and also to judge how satisfactory physical progress actually was. He should then compare the result with that obtained by inspecting the Grid record in Fig. 1.

As an objective and indeed most effective test of how impossible it is to deduce really definite or significant answers to these questions from mere inspection of this or similar tabular listings of routine data on height, weight, and age, one should try to do so with the set of numerical

values given in Table I. An experienced observer will be able to discern that the boy is average; with the aid of a standard height-weight table he would be found not far off center. But it is safe to say that not even the most experienced can detect the actual and important changes that have taken place during the period of observation in spite of the continuous and apparently steady increases in height and weight shown in Table I. Failing to attract attention, the boy would, as he actually did, pass unrecognized, in spite of the undeniable indications in Table II that he has not been doing well for almost three years.

TABLE II

EVALUATION OF PHYSICAL STATUS AND PHYSICAL PROGRESS IN THE CASE OF T. B. FOR THE AGE PERIOD 7 TO 12½ YEARS, SHOWING THE IMPORTANT NET EFFECTS WHICH MAY BE MEASURED FROM, AND WHICH ARE DISPLAYED BY, HIS GRID RECORD IN FIG. 1 BUT WHICH ARE NOT EVIDENT IN THE SAME WEIGHT-HEIGHT DATA LISTED IN TABLE I

ATTRIBUTE	EVALUATION AS OF FINAL POINT AT 12½ YEARS
I. Physical status	Still "good" but precariously near and rapidly approaching "fair" (B_2)
a. Physique	Loss of 1¾ channels
b. Development	31.5 per cent "off" by failure to achieve more than 24 of 35 expected units in the last 3 years
c. Nutritional grade	Departs -13½° off channel course. This is far beyond the maximum allowable departure of -8° from the optimal gradient as represented by the pitch of the channel system (54° 28′) in the scale of the three color grids; the departure, in fact, is eleven times the standard deviation (1.2°) of the direction of "healthy" curves that proceed channelwise
II. Physical progress	
a. Channel course	Up-channel from level 50 to level 87; thence cross-channel to level 113
b. Auxodromic progress	Perfectly satisfactory from 7 to 9½ years; entirely unsatisfactory from 9½ to 12½ years; should have reached level 113 at 12½ years. Developmental advance therefore shows lag of 11 level lines equivalent to specific retardation of 0.9 to 1 year behind his own schedule

This inherent risk of error in attempting to judge physical condition either by clinical methods or from a list of body measurements is tremendously reduced, if not completely eliminated, by plotting the very same data given in Table I on a Grid. The result is shown in Fig. 1 from which all the information summarized in Table II can easily be obtained. In fact, the main story of physical development is now concisely and informatively displayed. What cannot be visualized in the original table of heights and weights—namely, that growth and development had not been satisfactory—is seen at once from the curves as they traverse their own course among the Grid standards in the background. This is so chiefly because one is now able to take note of changes in physique, development, nutritional grade, and in physical progress directly and because these, rather than heights and weights, form the framework for an appraisal of physical condition.

It is usually astonishing to those who have had but few occasions to test the matter that so much important and vital information or changes of such magnitude as those shown by the Grid record and summarized in Table II can actually be camouflaged in the simple set of heights and weights given in Table I. From the standpoint of the whole problem of how to assess the physical condition of children and especially of how to find and identify the child who needs attention, in order to prevent further and quite unnecessary injury to body tissue, it is very important to see how easily a boy like this will be missed by ordinary methods of appraisal.

Weight and Weight Gains.—In the first place, according to the usual height-weight-age tables, T. B. would certainly never be considered underweight,* even at the last observation when he lacked only four pounds of what the tables call for. This is just less than 5 per cent off weight, and comes well within the limits of –7 or –10 per cent commonly adopted in practice. At no point, therefore, would the tables have selected him for examination or check-up.

Secondly, in spite of the fact that a weight curve may be quite misleading for the purpose of assessing the physical condition of a child because it can give no information on physique or on change in physique as weight increases, considerable faith is still placed in this method of appraisal.† The argument is usually put forward that so long as a child

*The concept of underweight has frequently done much harm. It overlooks all that is fundamental to a correct interpretation of growth, development, and physical fitness in children. It has not entirely vanished from clinical usage; one hears it frequently as a presenting complaint for an ailing child, but it appears, occasionally, in an inverted form under the designation weight-age or height-age.

The only pertinent question is *underweight with respect to what?* If reference were always made, as it sometimes is, to the fact that a child is underweight with respect to himself, the idea would be quite correct, though a method for determining this would still be required. What is usually done, however, and this is quite unjustified, is to consider a child underweight when the weight is less than some customary or arbitrarily chosen average, as though every child should weigh exactly what that average, however established, calls for. Reference to central or mean values of this kind is precisely what should and must be avoided, because this procedure makes no allowances for individual differences in body build, in developmental trends, or for other important attributes that define the physical condition of children.

†While weight, taken by itself, has long been recognized as an inadequate source of information by which to judge the physical condition of children, especially during school life, the thought and hope are still current that successive weights plotted as a curve with respect to age (often erroneously called growth curves) would make up the deficiency. The unquestioned and long established advantages of weight curves for infants have very likely done much to promote this form of graphic follow-up for observations on older children as well. From a weight curve, moreover, it is possible to obtain an approximate estimate of the rate of gain in weight. This, to be sure, helps to throw somewhat more light on the character of the weight changes, but unfortunately not enough light to aid the clinician in assessing the significant features of growth and development.

In fact, the very gain in information that appears at first sight to be invaluable to the analyst or statistician may even lead the clinician astray unless he is on guard; for what has not been clearly understood by those who advocate the use of weight curves as an objective means of physical appraisal in older children is that these weight curves give absolutely no indication as to whether a child's physique has been altered or whether it has remained the same during the interval in which the weight has changed.

Now evidence on this point is vital to the matter of assessing the physical condition of children, yet it cannot be obtained from a weight curve, simply because physique cannot be measured by weight alone. But this defect in weight curves is not their greatest drawback. They may, in fact, be quite misleading and the danger of this, astonishingly enough, is actually greatest precisely during an interval in which the child appears to have made a satisfactory gain. An everyday example is sufficient to show how unreliable curves of this kind are.

Consider a boy (P. K., 5427) who weighed 61½ pounds at 9 years and 69¼ pounds at the age of 10 years, his gain therefore being seven and three-quarter pounds for

(Cont'd on next page)

continues to gain weight regularly, there can be no serious question about the satisfactoriness of his growth. A good many things, however, would have to be considered under the broad term regularly and much will also depend on the choice of an acceptable standard with which to compare both weight and rate of gain in weight. But apart from the chief drawback already mentioned, that weight by itself cannot define physique, one should, logically, compare a given weight curve with a standard that represents about the same maturity class as that of the subject in question, provided that there were at the time some way of knowing which class he belonged to without having to wait for actual maturity to appear. In addition, one should also choose a standard, if possible, that represents the racial and socio-economic characteristics of the subject. These conditions, to be sure, cannot easily or always be fulfilled; and even if they could be satisfied, comparisons would still be without real value because no weight curve can reveal what is happening to physique.

With these limitations in mind, it is nevertheless interesting to observe that the weight curve of T. B. is practically identical, point for point, with that given by Richey[4] for his maturity group III, as well as with the curve described by Shuttleworth[5] for weight in boys selected on the basis of having their maximum increment in height at 15½ years. On the other hand, T. B.'s curve from the age of 7 years to slightly beyond 10 years follows the trend of average weight derived by Wetzel[6] on the basis of mass statistics. Thereafter it deviates by falling about one-half year behind that standard just as the two foregoing maturity curves also do. Finally, T. B. was obviously below Gray and Ayres'[7] California private school children but, interestingly enough, almost exactly one standard deviation below them at every age.

All the foregoing results indicate that T. B. could not possibly be selected for examination on the basis of his weight, because he happens to fall within the ordinary statistical limits of variation. These, more-

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the year. The gain was steady and not by spurt. Now, so far as anyone could tell from these data he would appear to be even somewhat heavier than a 9- and 10-year old boy according to almost any standard, and his gain for the year would also appear to have been fully up to expectancy for weight and age. In fact, this segment of his weight curve would appear to be ideally placed and nothing more would seem to be desired. On this basis he was pronounced "good" and not in need of further check-up.

What, however, are the possibilities of error? The answer is, indefinitely great, for the boy in question showed merely one of innumerable responses that cannot be detected in a weight curve. His height at 9 years was 51¼ inches, at 10 years, 55½ inches. What this actually signified is disclosed at once by plotting both his heights and his weights on a Grid. He had in fact undergone a tremendous change in physique from medium to a definitely linear build; his nutritional grade over the year had, accordingly, changed 18° off course, and he was well on the way to impending and obvious malnutrition at the age of 10 years, in spite of the apparently good but wholly illusory appearance of his weight curve. Thus, unless a physician has evidence to show what has happened to a child's physique during a given interval, he will have no completely objective basis on which to measure and determine what is referred to in clinical terms as that child's nutrition.

There are a number of other objections to the use of weight curves for the purposes of appraisal, such as the wide range of variation, long a stumbling block in actual practice, and again the untenable implication that a child should come up to a certain weight regardless of other matters. But these are minor details in comparison with the real danger that weight curves can be very deceiving.

These difficulties clearly illustrate the fundamental difference between having simply data and having information. In the case of growth and development, the full information contained in data on weight is not disclosed until weights are coupled with heights and thereby transformed into physique, development, and nutritional grade. This is the information that is needed for the appraisal of physical status, as outlined in Step I.

over, have long been known to be so unduly wide that weight itself cannot be relied on for the purpose of selecting a child who is actually in need of attention or for the purpose of judging his physical condition as accurately as desirable. At his very worst, T. B. was not more than 5 per cent underweight and this, in actual practice, is everywhere acknowledged to be within the so-called normal range. Nor could he have been suspected or picked out on the basis of weight gains unless one also chose every other boy whose gain at 11 or 12 years amounted to no more than six or seven pounds a year. Thus, clear evidence that the boy had lost physique and that he was actually pursuing a course toward ultimate malnutrition could not be obtained by comparing his weight or weight gains with various standards. At best the evidence is ambiguous.

Tuxford's[8] *Index.*—Owing largely to the uncertainties of clinical appraisal and also to the same difficulties regarding weight and increments of weight just now encountered in the case of T. B., many proposals have been made to deal with the problem of assessment by combining various body measurements and expressing the result in the form of an index. In the wide literature on the subject these have been variously referred to as indexes of nutrition or, again, of body build. On the whole, they have not been successful in helping to pick out the child who is under par. Tuxford's index,* which Jones[9] employed in a very thorough and enlightening study of this entire question, has recently appeared to be more promising than any other in providing an objective measure of what is called a child's state of nutrition.

By applying Tuxford's index to the data in Table I, purely for the sake of comparison, one obtains the following successive values:

At age 7.0 years	1.021	At age 10.75 years	1.067
At age 7.6 years	1.041	At age 11.25 years	1.056
At age 8.0 years	1.060	At age 12.25 years	1.056
At age 9.5 years	1.078	At age 12.50 years	1.036

But the lower limit of the normal zone is fixed at 0.960 by Tuxford himself, and at 0.970 by Jones, (readings being taken to the third decimal place), and the value for average children is roundly 1.000. It is therefore evident that T. B.'s state of nutrition was not sufficiently affected to be identified by the index.

While on this point, however, it is instructive to see which values of height or weight would have succeeded in lowering the values of the index to 0.970. A simple calculation from the data at 12½ years shows that

for a weight of 77 pounds, height would have to be 60½ inches, or
for a height of 56¾ inches, weight would have to be 72 pounds,

in order to reduce the boy's index to 0.97. In the former case this would place him on the border between the B_3 and B_4 Grid channels, at level

*Tuxford's index for boys:

$$\frac{\text{weight (kg.)}}{\text{height (cm.)}} \times \frac{381 - \text{age in months}}{54}, \text{ or } \frac{\text{weight (lb.)}}{\text{height (in.)}} \times \frac{379 - \text{months}}{300}.$$

Jones,[9] however, multiplies the results by 1,000 to eliminate the decimal point.

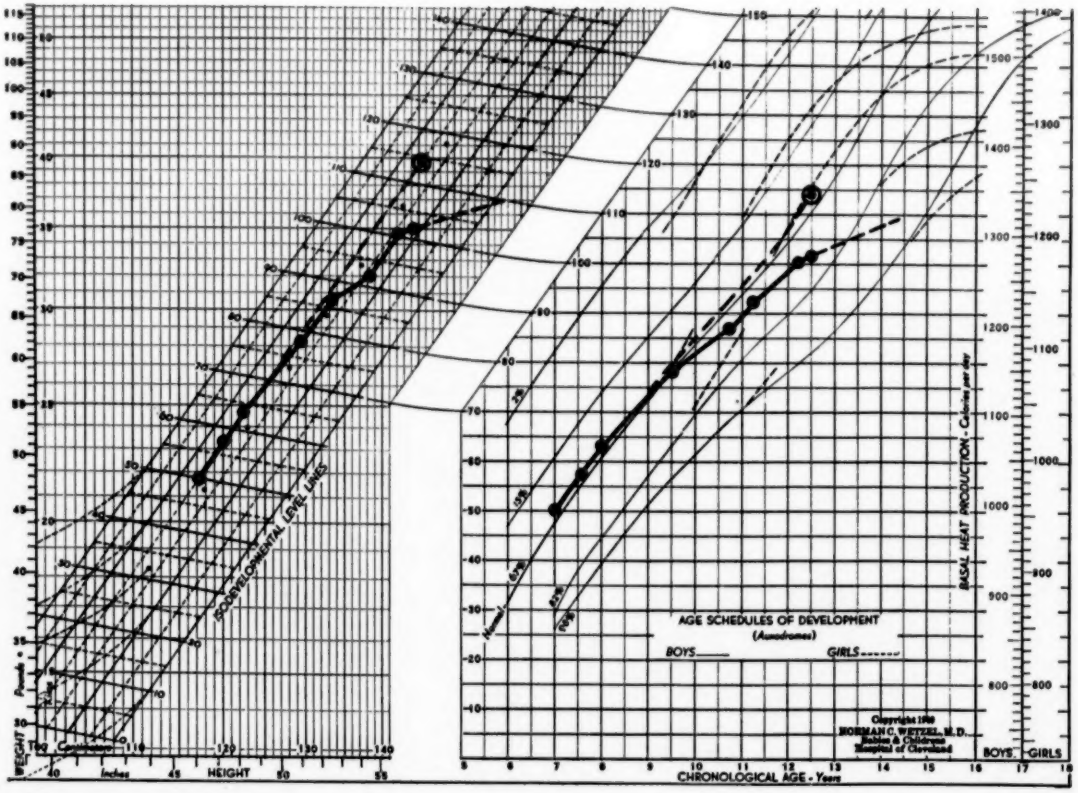

Fig. 1.—The Grid record of T. B., demonstrating failure in growth and development between levels 87 and 102 (ages 10¾ and 12½ years). The "drifting off course" and "behind schedule" which is easily visualized here but not in the data of Table I forewarns of oncoming malnutrition which could not be detected by clinical means, from height-weight-age tables, or with Tuxford's index. Broken line projections leading to level 113 along the border between channel A_1 and M and along the 67 per cent standard auxodrome indicate the course of development the boy should have taken on the basis of the first three or four observations. His recovery is described in another paper[10] that deals with malnutrition as a problem of failing growth and development.

TABLE III

POINT-TO-POINT EVALUATION OF PHYSICAL STATUS AND PHYSICAL PROGRESS OF T. B. (COMPARE FINDINGS WITH CURVES IN FIG. 1)

	PHYSICAL STATUS				PHYSICAL PROGRESS							
						AUXODROME						
									ADVANCEMENT OR RETARDATION			
AGE (YR.)	PHYSIQUE	DEVELOP-MENTAL LEVEL	NUTRITIONAL GRADE	OVER-ALL ESTIMATE	CHANNEL COURSE	LEVEL REACHED	LEVEL EXPECTED	DIFFER-ENCE†	DEVELOP-MENTAL RATIO	SPECIFIC (FROM OWN SCHEDULE) (YR.)	FROM 67 PER CENT SCHEDULE (YR.)	NET APPRAISAL
7.00	A_1-M	50	56°51′—Optimal	Good	Up-channel	50	–	–	7.2 / 7.0	–	+0.20	Satisfactory
7.60	A_1-M	57½	53°38′—Optimal	Good	Up-channel	57½	57½	0	7.8 / 7.6	0.00	+0.20	Satisfactory
8.00	A_1-M	63	51°8′ —Optimal	Good	Up-channel	63	63	0	8.2 / 8.0	0.00	+0.20	Satisfactory
9.50	M	78	53°7′—Optimal	Good	Up-channel	78	80	-2	9.5 / 9.5	-0.20	±0.00	Satisfactory
10.75	M	87*	34°10′—Too low	Good	Cross-channel	87	93	-6	10.25/10.75	-0.70	-0.50	Questionable
11.25	B_1	92	55°12′—Optimal	Good	Up-channel	92	98	-6	10.75/11.25	-0.70	-0.50	Questionable
12.25	B_1	100½	13°45′—Extremely low	Good	Cross-channel	100½	109	-8½	11.6 /12.25	-0.85	-0.65	Unsatisfactory
12.50	Low B_1	102		Good approaching Fair (B_2)		102	113	-11	11.7 /12.50	-1.00	-0.80	Very unsatisfactory

*Course of development between levels 87 and 102 has an inclination of 41°, or 13½° less than the optimal gradient.
†Negative differences measure what is described in the text as developmental lag.

104, and in the latter case into the B_2 channel, very near to B_3, at level 96. But while either of these positions on the Grid would signify as soon as plotted that examination and inquiry were required, they are both rather distant from the boy's actual position in channel B_1 at level 102.

The foregoing example of T. B. thus shows how an ailing child may be detected by the Grid method of converting weights and heights into the essential features that characterize individual growth and development. The results are positive and they cannot be easily challenged, as frequently happens when appraisals are based chiefly on subjective impressions or on the use of tables and indexes. The immediate value of an objective record such as that provided by the Grid is obvious. It reveals at a glance how well or, as in the case of T. B., how poorly the child has been getting along, in spite of the fact that his physical status had not yet fallen off sufficiently to lead him into the "fair" or B_2 channel.

The paramount importance of comparison with self—that is, of determining the boy's own par and of having a simple method of applying this principle—is clearly illustrated by the curves shown in Fig. 1. But it should again be noted that the principle *each child his own standard of comparison* has been put fully to work, not on weights and heights primarily, but rather on all those pertinent attributes (physique, development, etc.) listed under Steps I and II, which first require evaluation before any sound estimate of physical condition can be rendered.

Thus far the purpose of presenting the case of T. B. has been twofold: (1) to show how little a set of weights and heights actually reveals when they are viewed in tabular form and (2) to show how the same data plotted on a Grid and thus converted into the basic elements involved in Steps I and II enable the physician to measure small but significant departures from satisfactory progress long before these can be recognized by other means. Thus far, also, the episode of T. B. between the ages of 7 and 12½ years has been treated as a whole. For the purpose, however, of giving a further illustration of how this method enables a physician to appraise the physical condition of children, it is worth while to examine the Grid record of this boy in detail.

POINT-TO-POINT EVALUATION

When the data in Table I are plotted as in Fig. 1, it becomes possible to evaluate each point in terms of the elementary components that constitute the two chief items, physical status and physical progress, outlined under Steps I and II. The results in the case of T. B. are brought together for brevity and convenience in Table III. The separate evaluations should be compared with the corresponding points in the Grid record of Fig. 1.

In actual practice it is unnecessary to tabulate the findings as is done here, since familiarity with Grid records soon enables one to obtain a better impression of the results by reading the curves directly than by a time-consuming study of a table.

PHYSICAL STATUS*

The over-all estimate of physical status at every point from the first at the age of 7 years to the last at the age of 12½ years is "good," because the boy at no time moved out of the three center channels A_1, M, or B_1, in spite of the fact that he did change channel placement from high M or on the border of A_1 and M to B_1.

Children in any one of these three center channels are overwhelmingly rated as of good physical status when they are examined by physicians. What clinicians refer to as nutrition is always acceptable in these children, although close inspection of them will reveal that rotundity of contours, especially about the neck, shoulders, scapula, arms, and thighs, tends to be just distinguishably greater among the typical A_1's than among the M's, and again greater among M's than among B_1's. In other words, body bulk and robusticity are not in question among children whose points plot in the three center channels. On this basis it is easy to understand that T. B. is to be rated as of good physical status for every point from that at 7 years of age to that at 12½ years, though the rating for the last point may be qualified by remarking that the boy is approaching "fair;" that is, the B_2 channel. Strictly speaking, such a rating, however, encroaches somewhat on the matter of progress; from the purely technical point of view it is perhaps best to keep to the rule that any point in B_1 represents good physical status, because the chance for any child in B_1 of actually being good is better than 19:1.

While the over-all estimate of physical status is thus taken to be good at each point for T. B., it is nevertheless evident that the channel

*As frequently employed, the term nutritional status is a misnomer. A portion but only a portion of what is intended and implied by this term is fully contained in and correctly described by the term physical status. This distinction must be emphasized and it must be understood if one seeks to disentangle the real from the unreal elements in the problem. Its use, whether intentionally so or not, presupposes that a child's "status" is mainly a matter of food. A physically run-down child, however, cannot always make the best use of good or proper food any more than a disabled furnace can effectively utilize the best coal. Yet, because better food has helped to improve the physical status of many children, too much emphasis is often placed on diet, and attention is correspondingly withdrawn from the child himself. In him, however, faulty hygiene, infections, metabolic or endocrine disorders, and even emotional or social maladjustments may frequently be far more important and direct causes of trouble than improper food habits.

There is, in addition, another though a much subtler objection to the concept of "nutritional status" as applied to children. In the case of adults this term referred originally to how well or how poorly nourished a subject might appear to be. Such estimates were based on direct attempts to determine whether illness had produced wasting of body tissue. But in an adult, good food and its proper utilization serve only to maintain his status or comparatively fixed position. In a child, however, food must maintain growth, not status in the sense of fixed position.

Thus, so far as children are concerned, the expression good nutritional status is by no means the counterpart or equivalent of being well nourished. Its use has been largely to blame for the failure of many to perceive that the most important affair of childhood—growth and development—is anything but static. Consequently, all efforts and methods designed or employed to estimate "nutritional status" are bound to backfire—owing primarily to the contradictions contained in the terms nutritional, status, and growth. The term physical status, on the other hand, is not so encumbered and refers merely to the state or condition of a child at any given moment. In the Grid technique physical status has been specifically defined to represent the over-all and combined effect produced at a given moment by the processes of growth, development, and nutrition acting on a child of given physique.

shift and the consequent lowering of nutritional grade have progressively led to a cumulative change of 1¾ channels by 12½ years of age. Physique has accordingly changed also, but again from the standpoint of an over-all estimate the total change has not yet been sufficiently great to throw the boy into B_2 where it is safer, on the basis of clinical trial, to evaluate a child's physical status as fair rather than as good.[2]

From 7 to 10¾ Years of Age.—The values for the three components of physical status at 7.0, 7.6, and 8.0 years (Table III) are clearly such that there is no distinction, save the proper differences in level between them. Nutritional grade even up to and including the value at 10¾ years is directly up-channel, the point here being only ½ channel removed from the upper border of *M*. In most instances such a departure by itself could mean or indicate little; even here it becomes significant not because of itself but rather because of the fact that the boy took fifteen months to travel the 9 points between level 78 and level 87. Again one encroaches on the domain of progress in making this observation.

From 10¾ to 11¼ Years of Age.—Somewhat similar remarks apply to the immediately following segment between 10¾ and 11¼ years of age; that is, between levels 87 and 92. Here the shift in nutritional grade has been sufficient to place the boy definitely across the line into B_1, a loss of just more than ½ channel in only 5 levels of advancement. But since normal variations do not allow more than ½ channel in 10 units of advancement, the value for the gradient of this segment is therefore suboptimal.

From 11¼ to 12¼ Years of Age.—The next segment represents the course of development between 11¼ and 12¼ years of age and an advance from level 92 to level 100.5. Since the value of the nutritional gradient is here practically up-channel, it will be clear that physical status throughout this interval had been, on the average, slightly but definitely better than in the immediately preceding segment. The total change between levels 92 and 100.5 is, however, only 8½ units, or about 70 per cent of the average advance for one year represented by the usual rule, "a point (or level) per month."[2] Thus, although the inclination of this segment is, for all practical purposes, strictly up-channel, one can nevertheless detect a lag in advancement which must ultimately be taken into consideration; but here, again, lag belongs properly to progress rather than to status per se. More noteworthy in relation to the previous segment are the facts (1) that the curve proceeded along the upper margin of B_1, (2) that it did not, throughout the year between the ages of 11¼ and 12¼ years, continue at the low gradient of the preceding segment, and lastly (3) that it did not, however, return to channel *M*, as happens when early, simple malnutrition is successfully treated.[10]

Thus physical status from 11¼ to 12¼ years of age remained, on the whole, good and, by virtue of a more nearly optimal trend throughout this period, just recognizably better than in the preceding half year.

At 12½ Years of Age.—The final values at the age of 12½ years signify that physical status though good is precariously close to fair. Notable, once more, is the difficulty of keeping the analysis strictly on the plane of status without entering upon considerations of progress. But, so far as the final point itself is concerned, one would again classify physical status here as good with the qualification that one component, nutritional grade up to and (apparently) including the final point, is definitely suboptimal.

PHYSICAL PROGRESS

By studying the relations between sequential states, one arrives at an interpretation of physical progress. The general over-all picture of progress depends, however, not only on the trend of the curve in the channels but also on the trend of the corresponding auxodrome. The former, to be sure, is directly a manifestation of nutritional grade and thus helps to connect one state with another. In the channel course, however, time is submerged, so to speak, because one cannot determine from the length of a given segment how long it took to traverse that segment. Yet rate of advance and elapsed time are obviously very important matters in growth and development, and an evaluation of physical progress cannot be made without taking them directly into consideration. This is accomplished by means of a child's own auxodrome which simply shows how long he has taken to proceed from one point to another.

Channel Progress.—Individual ratings on the course of development as measured along the path traced through the channel system are given in Column 6 of Table III. The unusual deviations are those in which the curve progresses across rather than along the channels. Such a deviation signifies that development is taking place in part at the expense of physique which itself is changing from an A_1–M to M and ultimately to B_1. The total effect throughout the five and one-half-year period has been a shift of 1¾ channels, all of which took place during the final three years. The first two and one-half years, on the other hand, illustrate the common finding that healthy children pursue a channel course as though this were a preferred path. Subsequently the persistent departure toward the lower side of the channel system is just as prominent a feature as is the straight-on channelwise course from 7 to 9½ years of age. There can be but one conclusion; namely, that the circumstances of the boy's life which prevailed initially were changed, and changed radically, during the latter part of the period of observation, for the cross-channel departure starting at 9½ years of age far exceeds those comparatively minor fluctuations which the curve of a healthy child displays as it continues up-channel, much as this boy's own curve did between the ages of 7 and 9½ years.

The manifest and significant change in channel course is an item that cannot be detected in the original data of Table I (though it obviously resides there) any more than a photographic image can be seen in an

exposed but undeveloped negative. But even more important than the impossibility of detecting an unfavorable trend in ordinary records of heights and weights is the danger that the usual methods of evaluating heights and weights may actually be misleading, as they were here, for at no time, not even at the very last observation, would T. B. be conconsidered more than 5 per cent underweight.

Under conditions of normal growth and development, successive departures tend to balance each other, the result, accordingly, being a curve that carries out the inherent tendency of children to develop up-channel and hence without significant change in physique. But the successive departures off channel in the case of T. B. are not compensated, though there is a slight suggestion of "improvement" in the segment between levels 92 and 100.5 (11¼ and 12¼ years). The latter half of his channel curve veers –13.5° away from its original direction. A departure of this magnitude, especially when so persistently maintained, is always significant. It calls for thorough investigation, because the maximum allowable departure which corresponds to the loss of only ½ channel per 10 levels of advancement is 8° in a Grid, and the actual departure is therefore more than eleven times the standard deviation (1.2°) of the direction of healthy curves proceeding channelwise.

The explanation in the present case is to be found in the family circumstances, since the boy, his mother, and three other children were obliged to go on relief when he was 9 years old. Yet it should be remarked again that his physical status had not suffered sufficient degradation to direct him into channel B_2 in spite of the comparatively great change plainly visualized in the channel curve between levels 78 and 102. Alterations in nutritional grade thus become sensitive indicators which can foretell physical disturbances that meanwhile remain surreptitiously in the making.

Auxodromic Progress.—The idea of physical progress is somewhat more obviously related to time and age than it is to the directional changes which have just been discussed in connection with the path that the curve of development traverses in the channel system. What one chiefly wishes to know in this regard is: How far did the child progress (develop) in a given period of time? And as a corollary: How far should he have progressed? Both of these questions are answered for the case of T. B. in the seventh to twelfth columns of Table III. These have been set up by taking readings from the boy's *actual* auxodrome in Fig. 1 for levels reached; from the projection of his originally established auxodrome for levels expected; and, lastly, from the neighboring 67 per cent standard for the developmental ratios and for estimates of retardation.

An individual child's auxodrome is constructed in the right hand panel of a Grid, as originally explained,[2] simply by plotting the value of the developmental level corresponding to each weight-height point against the age at which that level had been or is reached. Levels are read from

the diagonal scale along the channel system. Thus, T. B. reached level 50 at 7 years, level 57.5 at 7.6 years, level 63 at 8 years, and finally level 102 at 12.5 years.

The boy's complete auxodrome shows two main effects: (1) an unmistakable tendency to parallel the adjacent 67 per cent standard auxodrome during the earlier years from 7 to 9½ and (2) an equally remarkable tendency during the later years to deviate from its original direction by falling continuously farther behind *itself* as well as behind the 67 per cent standard. The early period, in other words, showed satisfactory physical progress; the later period, on the other hand, more and more unsatisfactory progress. This is the broad conclusion to be derived from surveying the trend of the boy's auxodrome as a whole. A more detailed point-to-point analysis and measurement of progress is given in Table III, the numerical values of which may be compared with the more easily visualized trend given by the boy's auxodrome itself in Fig. 1.

Attained and Expected Levels of Development.—These are compared in the seventh and eighth columns of Table III. The expected levels at any given age are read (after the age of 8 years) from the dotted projection which parallels the 67 per cent standard and which, like the original branch of the boy's actual auxodrome, is continuously about 0.2 of a year in advance of the 67 per cent standard. Had T. B. therefore continued to carry out his development on the particular schedule which is indicated by the first three points at 7.0, 7.6, and 8.0 years, inclusively, his auxodromic advance would have coincided with the dotted projection, and he would have reached level 80 instead of 78 at 9½ years; level 93 instead of 87 at 10¾ years, and so on until he had attained level 113 instead of level 102 at the final age of 12½ years.

In three years he had thus accumulated a net deficit of 11 levels, or to express the same result somewhat differently, he had fallen 11 units behind in his development during a period in which he should have advanced 33 levels from 80 to 113, whereas he succeeded in completing only 24 of these. This, again, is a most important finding that cannot possibly be discovered by simply looking at the original height-weight data in Table I. Yet with the same data plotted on a Grid and thus converted into units of development (among other things), it is easy to discern even the earliest signs of lag in physical development, which made its first appearance in T. B. at the age of 9½ years. To be sure, he failed at this time by only 2 units to reach his expected level of 80, and this alone would hardly have been considered significant. Subsequent observation, however, showed no tendency to make up these 2 levels; it indicated, instead, that lag was actually increasing, for in the fifteen months following the age of 9½ years he advanced only 9 levels, or about 60 per cent of average expectancy, which calls for 1 level of advancement per month.

Such progress is at least questionable if not definitely unsatisfactory and has been so indicated in the last column of Table III. It is very important, moreover, to note now how sensitive an indicator a child's auxodrome can be, for lagging development and the consequent loss of schedule between 9½ and 10¾ years actually set in while the boy was still traversing the very center of the *M* channel and thus quite definitely before he had changed physique enough to drift over into B_1. As previously remarked, these are observations that cannot possibly be made from an ordinary weight curve because there is nothing in such a curve to indicate what is happening to physique.

DEVELOPMENTAL LAG

Developmental lag as detected from the plotted auxodrome is apparently the earliest sign which forewarns of oncoming malnutrition. It is seen with convincing regularity in the records of underprivileged or poorly managed children, and its meaning can be clearly substantiated by careful inquiry and examination. Rarely will such evidence fail to support the conclusion that the child in question "has not been doing as well as he should be."

Final proof of the true significance of lagging development depends on the response which is observed when the child has been placed under acceptable conditions of life, diet, and hygiene. A child with a lagging auxodrome, the cause of which may be traced to improper or insufficient food, will respond promptly to simple but obvious remedies and no special fortification of the diet will be required to put him back on his proper schedule. When lag, however, is the result of disease or is due to even more remote causes, it will not be removed by ordinary measures. A more extended discussion of auxodromic lag in simple malnutrition and its prompt response to treatment is given in another paper of this series.[10]

It is especially interesting in the present connection to note that precisely the same phenomena that characterize the developmental progress of T. B. can be demonstrated in the most recent data of Stuart and Kuhlmann[11] on French children in Marseilles. The channel course of the French boys, as plotted from average values of the group, remains well within A_1 and *M* up to 9 years and crosses into but not beyond B_1 by the tenth year, thus matching the physique of the California controls; but the corresponding auxodrome fails by 15 units to reach its expected level of 86 at 10 years. Since these French boys, as estimated from their averages, happen quite fortuitously to be on the same age schedule of development, that is, on the same original auxodrome as T. B., it is easy to see that his developmental lag was much less than theirs, because he at age 10 was not more than 4 units behind the same expected level which they failed to reach by 15 units at the same age.

What this combination of findings actually signifies in the case either of T. B. or of the French children is simply that any circumstances

which produce undernutrition lead first to a slow down in the rate of development, manifested in part as lag, and only later, when it is sufficiently severe, to bodily effects that culminate in gross changes in physique. Such findings, of themselves, are enough to put the traditional concept of nutritional *status* entirely out of court.* On the practical side, moreover, they help to explain the frequent discrepancies between the suspicion of "trouble" on the one hand and the failure to demonstrate it on the other. For an occasion of this kind it may prove helpful to remember that a child can actually be lagging behind in his development even though he has not at the moment lost sufficient ground to place him in a questionable channel, such as B_2 or still less into B_3, where his physical status would be recognized, with little exception, as obviously borderline or even poor.

So long as children remain in any one of the three center channels the chance of finding physical evidence of undernutrition is exceedingly small, especially by ordinary clinical methods. Yet, as the case of T. B. clearly shows, the first and at the time the only telltale indicator that all was not going well was to be found in his developmental lag. This result demonstrates the great practical importance of looking beyond matters of pure status and of taking developmental progress into immediate consideration before an appraisal of physical condition is rendered.

To neglect an evaluation of physical progress is to invite potentially dangerous and unnecessary delay. The appearance of lag in an auxodrome is the signal for attention; it is a warning that none can sense in a list of heights and weights, yet one which all can see in a plotted auxodrome.

SPECIFIC DEVELOPMENTAL RETARDATION

Thus far physical progress has been evaluated only by comparing the "expected" level of development with that actually attained. The difference between these values has been referred to as developmental lag. In T. B.'s case lag is shown by the fact that the levels which he reached on and after the age of 9½ years were always behind those he should have attained. Had the opposite been true, namely, that he had advanced to levels higher than or ahead of those expected, the difference would have been called developmental lead. Now, it may also be seen (Fig. 1) how T. B.'s developmental lag is directly revealed in the auxodrome panel by the vertical distance between the expected and the actual branches of his auxodrome after the latter has changed its direction away from continued parallelism with the standard schedules of development.

But, besides revealing lag, such an auxodrome also discloses developmental retardation, and it is easy to see that *lag* and *retardation* are neither synonymous nor identical even though they both refer to and actually measure the same fundamental effects that give a clue to the

*See footnote on p. 93.

nature of physical progress. To avoid possible confusion it is convenient to draw the following distinctions: Developmental lag refers simply to the number of level lines a child has failed to achieve as reckoned *vertically* from his "expected" schedule or auxodrome, whereas developmental retardation represents the length of time required to produce that lag as reckoned *horizontally* from the same expected schedule. Actually, retardation is the time equivalent of lag; it is essentially time lost which can be made up by overcoming lag. If this is accomplished, the child is back on schedule.

It is necessary in addition to qualify retardation so defined as *specific* retardation because a child who is usually referred to as "retarded" is one who has failed to develop to a level expected of the general mass of children, irrespective of whether he is self-retarded or not. The matter of retardation is thus always a relative one, but ambiguity as to which of the two possible meanings is intended or implied can also always be avoided by understanding that specific retardation is estimated with respect to a child's proper auxodrome and that it signifies, as in the case of T. B., deceleration in physical development, which always results in throwing a child behind his regular schedule of development.

Development Relative to the 67 Per Cent Standard Auxodrome.—It is generally acknowledged and understood that certain children are more "advanced" than others of the same age. Even in the absence of a direct measure of this, it has also been understood that an advanced child would be considered so not by virtue of greater weight or greater height, alone, nor only because of greater all-round size at a given age. Such a child is presumed, in addition, to be closer to the final goal of growth as it is represented by the average size of the adult population.

The difficulties of measuring what is almost immediately obvious on simple inspection of advanced children have been handled in the Grid technique, first, by separating out of a given combination of height and weight the component that measures physical development as distinguished from the component that measures physique; second, by defining the general pattern of development with respect to increasing age in the form of the family of five standard auxodromes to which individual auxodromes will conform in health; and third, by calibrating these auxodromes or age schedules of development in percentiles to indicate the relative number of children that one may expect to find in the general population whose development equals or exceeds what a particular standard calls for at a given age.

Now, the 67 per cent standard auxodrome indicates the levels of development which two-thirds of children should reach on or before, and hence no later than, the corresponding ages to which it refers.[2] This auxodrome, accordingly, is a convenient reference line by which it is possible to estimate development relative to the childhood population at large. For example, a child whose own auxodrome coincides with the 67 per cent curve is thus neither retarded nor advanced so far as the

mass of children is concerned. A child who attains a given level at any age before that indicated by this demarcation line is relatively advanced. Conversely, a child will be relatively retarded if he attains a given level at any age later than that indicated by the 67 per cent standard.

From his seventh to eighth year T. B. is therefore rated about 0.2 of a year advanced because he reached each of the first three observed levels about 0.2 of a year in advance of the 67 per cent standard. During that year he kept to his schedule. Thereafter, however, as he became specifically more retarded by falling behind his own proper schedule, he also took up more and more retarded positions with respect to the whole population of children as his actual auxodrome crossed and then passed behind the 67 per cent standard.

Finally, at 12½ years of age he had become specifically retarded by 1.0 year but only 0.8 of a year behind the demarcation line which has been taken to separate advanced from retarded children. In this connection it may be noted (1) that the two figures for retardation can be identical only in the case that a child's proper auxodrome coincides with the 67 per cent standard; (2) that the difference between these figures has no special significance, whether large or small; and (3) that specific retardation can take place in an advanced child without likewise causing him to become retarded with respect to the mass of children. An illustration of the latter fact will help to explain the significance of both kinds of retardation that have been described.

Suppose T. B. had reached level 50 at 5 instead of at 7 years. Other things being equal he would then have reached level 102 at 10½ instead of at 12½ years. Now, however, although he would still be reckoned as advanced relative to the general population, because level 102 is not reached on the 67 per cent curve until 11.7 years, he would nevertheless have fallen behind his own hypothetical schedule by the same amount as before, and would therefore again have become specifically retarded as the result of self-deceleration of development.

The subordinate character of retardation relative to the population is further clarified by considering another possibility. A boy who, like T. B., has reached level 102 at 12½ years but unlike him has done so on an auxodrome that continuously parallels the family of standards would be judged, relative to the general population, as being retarded to the same extent as T. B., but he would obviously deserve a superior rating of progress because he had succeeded in keeping up with his own schedule of development whereas T. B. had failed to do so.

Thus progress that the child has actually been making compared with what he should have made, irrespective of whether or not this results in his being retarded or advanced as compared with other children, is the important observation.

The case of T. B. has shown how the general principle *each child his own standard of comparison* is and can always be applied to the matter of estimating physical progress. For this principle is clearly

evident in the simple but comprehensive rule that each child should keep to his own schedule of development. If he does, his auxodrome will parallel the standards; if he does not, it must necessarily undergo either specific advancement or specific retardation, regardless of its position relative to the 67 per cent standard. One of these three results is bound to take place; and that result, coupled with the course of events in the channel system, defines the quality and quantity of physical progress in unambiguous terms. From many standpoints, moreover, it is just as important to be able to demonstrate satisfactory progress as it is to detect unsatisfactory progress. Granting these objectives to be within the scope of the Grid technique, the value of periodic heights and weights and of a faithfully kept Grid record of them is clearly self-evident.

Progress According to Developmental Ratios.—As originally explained,[2] a child's advancement or retardation relative to the general population may be expressed in an alternative form by stating the ratio of his developmental to his chronologic age. Since a child's developmental age is simply that age at which the 67 per cent auxodrome intersects a given level, it is evident that *all children on the same level have the same developmental age.* The ratio of this to a child's actual age gives the corresponding degree of advancement for ratios greater than 1 and the extent of retardation when the ratio is less than 1. The quotient is not worked out formally by division in order to get the result into decimal form because this tends almost completely to bury the very information one seeks. What is wanted is to know how far advanced or retarded a child happens to be *at some particular age,* and this information is completely submerged if the decimal equivalent be given, as is routinely done in the comparable case of an intelligence quotient.

Thus, from the fourth last column of Table III it will be seen that T. B. had a developmental ratio of 7.2/7.0 at the first observation. One sees immediately that he was 0.2 of a year advanced *at age* 7. The quotient 1.028 (assuming 3 decimals to be valid) likewise shows very slight advancement but gives no idea as to whether this applies to a boy of 7 or of 12 or of any other age. Besides, it is absolutely improper to express a quotient to the third decimal when the original figures are correct to only 1 decimal. Hence the best that could be done here would be to give the result as 1.0, which would imply that the boy was on the 67 per cent auxodrome. Had he even been as much as ½ year advanced, that is, with a developmental ratio of 7.2/6.7, the quotient would be 1.075 which would have to be rounded off according to rule to 1.1, not 1.08, since only 1 decimal or a total of two significant figures are allowed in the result. Now the difference between 1.0 and 1.1 is also small and in considerable doubt, though the corresponding fact that the boy is one-half year advanced is by no means insignificant nor subject to the same doubt. For a healthy child who is one-half year advanced at 6 years of age will tend likewise to remain one-half year ahead throughout

his entire course of development. This is evident from the general parallel pattern of the five standards representative of the entire family of possible auxodromes.

A more complete discussion of developmental ages and ratios, especially in connection with the fact that developmental age by itself gives no hint or measure of maturity, is contained in another paper of this series.[12]

Successive developmental ratios, as indicated in the point-to-point values of Table III may be employed to indicate the character of physical progress, although their main usefulness is limited to a numerical expression of how far a child is advanced or retarded with respect to the general population. The change in successive ratios is explicit and shows clearly how the boy gradually lost his position of relative advancement to become fully 0.8 of a year retarded when he was 12½ years old.

NET APPRAISALS; COMPARISON OF TABULAR AND GRAPHIC EVALUATION

In the final column of Table III are listed individual net appraisals for each of the original observations. These summarize in a word or two the over-all results that are parceled out among all the twelve separate items in Table III describing physical status on the one hand and physical progress on the other. The dozen individual facts arrayed in line 2, for example, are lumped together in a nutshell and labeled "satisfactory," whereas the similar array in line 6 is "questionable," and that in the last line "very unsatisfactory."

These results are briefly expressed but by no means as briefly or as clearly as in the Grid curves themselves. The tiresome monotony of the table is completely avoided in the graphic picture of growth and development which is so much more succinctly displayed and more readily grasped in the Grid. The minutiae necessary to a tabular listing of all the important features seem, as it were, to blend together in the plotted curves just as one sees trees, not individual leaves, buds, branches, or bark. The columns and rows of the table contain, to be sure, the particular numerical or descriptive details that measure the important changes in physical status or progress, but there is rudely missing from them that indispensable effect of continuity by which the eye can detect each slight but definite change as the pattern of the boy's development unfolds itself. In the table there may be reasonable doubt about the possible acceptability of 1/10 year differences, or of ½ level of development; in the graphs of Fig. 1, on the other hand, some differences can be at once allowed for and others recognized as simply repeated evidence of a single unmistakable trend.

The final evaluation of the case from the table alone would be cumbersome even if convincing, time-consuming even if more enlightening than the entirely unrevealing heights and weights of Table I. But if the Grid technique actually required that such an enumeration of twelve

facts be made at every observation in order to render a net appraisal, there would clearly be little to commend it for general routine use; it would, instead, have to take its place among other laborious special procedures. On the contrary, however, each point as plotted, each segment as drawn succeeds in establishing an all-in-one result that contains the answer to the fundamental question in every physical appraisal: *Is the child in question growing and developing as well as he should be?* To be able to measure progress is an important advantage of the Grid technique, but to be able to demonstrate it so that its meaning is open to all is even a greater advantage. In the matter of prognosis, moreover, it may prove more significant at times to show that progress has been satisfactory than to detect unsatisfactory progress. This is especially the case when one is dealing with obscure ailments or, again, with frank disease, such as chronic rheumatic carditis in which one might expect, a priori, that growth and development would be more or less adversely affected.

But to appreciate fully how much more effectively the Grid curves show that T. B. had not been getting along as well as there was every reason to expect, one must compare the general picture of the graphs in Fig. 1 not only with the individual lists of details in Table III but also with the summarized results previously given in Table II. Even so, the total information contained in both of these tables falls short of conveying three impressions that are as unmistakable as they are immediate in the Grid curves: (1) the absolutely individual characteristics of the boy's growth and development portrayed in terms of all items involved in Steps I and II and in comparison with the untold possibilities among the general population, (2) the coordinated trend relative to himself, and (3) a clear and undeniable forecast of what is likely as well as of what ought to happen to him. Here, literally, is diagnosis and prognosis; not of disease, to be sure, but of growth and development. What is otherwise intangible and what has for this reason so often escaped direct attention or acknowledgement is now made easily accessible by the simple expedient of plotting out a child's Grid record.

To state that a boy in T. B.'s position should rightfully have been an A_1–M at level 113 instead of a B_1 at 102 when last observed is correct though unimpressive; but to *see* this simply by comparing actual with expected trends of development and progress is to overcome not only all reasonable doubt as to the result, but also any difficulties in visualizing growth and development at work. Here is an example in which words, figures, or lists of facts are of no more avail than they are in describing the path of a projectile, the characteristics of a sound wave, the properties of an electrocardiogram, or the concrete nature of any kind of motion. Since the eye can sense the integrated whole and distinguish regular from irregular progress, the significance of events may be grasped by almost a single "look at the map"; and in the particular case of growth and development, where landmarks are otherwise easily

obscured and not readily agreed upon, instant recognition of what is going on is an especial advantage that helps to explain abnormal departures to parents or teachers. The need for action is plain and it is plainly understood; indecision, doubt, and consequent delay, the bane of preventive health effort, are eliminated when parents and teachers are shown direct graphical evidence that the trend of growth and development has been unfavorable. Many of the difficulties which are commonly encountered in attempting to render health service are chiefly the products of vague and uncertain objectives. This will continue to be so until it is clearly recognized that physical appraisals in children must be based primarily on the study, measurement, and evaluation of growth and development rather than on a routine report of physical findings. Reports of this kind cannot stimulate cooperative action, partly because they are not generally understood unless signs and symptoms are obvious, partly because they show little at the time most favorable to action, but mainly because they do not, and cannot, give demonstrative proof as to how well or how poorly growth and development are proceeding.

CORRELATION OF GRID APPRAISALS WITH THE MEDICAL HISTORY, PHYSICAL FINDINGS, AND OTHER DATA

The net appraisals on T. B.'s growth and development have now been seen to fall definitely into two classes, satisfactory for the earlier period between 7 and 9½ years and entirely unsatisfactory from 9½ to 12½ years. The unfavorable trend of the later period is recognized as getting worse with the lapse of time, in spite of the fact that the boy had not lost sufficient ground to be picked out by ordinary methods of appraisal. Such a trend, as has already been remarked, must obviously stir up action for thorough inquiry. Had the Grid record been routinely kept, action would first have been started at 10¾ years of age, that is, at the time when he had fallen about 6 units behind his expected level of development, even though his developmental curve still coursed along the *M* channel. This is a good example of the kind of departure from the Grid standards that calls for investigation, for the basic rule governing assessments is simply that a child should keep to his channel, once this is established, as well as to his own specific schedule of development. Moreover, a lag of 6 units is equivalent, on the average, to the loss of six months in schedule. This is not negligible.

The proper time to initiate full investigation not only by means of physical examination but also into the boy's medical and family history would have been at the age of 10¾ years. Much emphasis is ordinarily placed, especially in describing the importance of school health programs, upon the value of thorough medical history, parent conferences, and family studies. Experience shows only too clearly, however, that routine histories, like routine examinations, have but limited worth, in

spite of the fact that both are sound in principle. Their chief drawback is that they are rarely either timely or pertinent. To be effective in throwing light on developmental problems (for this, after all, is the main purpose of a medical and family history), they must be initiated for cause, not simply to fill up the blanks in regular forms. Many a routine history, boiled down to solid fact, reveals no more than that the child is living. Unless there has been sufficient cause for thorough inquiry into particulars, there is neither time nor place to detail the habits and activities of a day, of seven days a week, or of the days of a year.

Consider the matter, however, the other way round, as, for example, when an examiner is confronted with the definite evidence of failure in development such as T. B. displayed in his Grid record at 10¾ years of age (level 87). Here is a challenge not only to do a good physical examination on the spot, to carry out special tests by proper referral, but also to have the boy's own medical and family history looked into thoroughly.

From the standpoint of physical examination, many findings that would otherwise be regarded as insignificant now take on direct and clear importance. To begin with, does the boy show any detectable physical signs of being under par? Here is the place to note lack of luster in the eye, as well as how scarce or how flabby subcutaneous tissues are. Here, too, much more meaning can be attached to a single carious tooth, and still more to several of these. Ragged tonsils, associated with granular hyperplasia of the pharynx, a coated tongue, obstruction to the nose, and enlargement of cervical lymph nodes all point to minor physical defects that are more definitely in need of repair than if they had been routinely noted.

Under many circumstances little will be found in the chest itself, though here again every method of examination must be employed to rule out evidence of disease in pleura, lungs, and bronchial tree. Similarly with the heart and circulation, where full confidence cannot be placed in a diagnosis by noting simply the presence or absence of murmurs. Cardiac enlargement must also be looked for and it might only be found by roentgenologic examination; if so, an electrocardiogram would be indicated, if not before. The value of determining the sedimentation rate should not be overlooked when one is dealing with definite developmental retardation, the cause of which is obscure, since a number of children with subclinical rheumatic carditis have been found who showed only developmental retardation and elevated sedimentation rates.[10]

A palpable spleen is another finding that might ordinarily be passed over, especially if the organ is soft, has a moderately sharp edge, and extends only one-half of a finger breadth or so below the costal margin. Coincidental increase in the number or size of the regional lymph nodes must be investigated in conjunction with a study of the blood, where

simple anemia must be thought of and looked for. Not one but several urine examinations should be included in order that the physical story can be unraveled.

Failure of the foregoing efforts to disclose a set of findings that can reasonably account for a Grid record of unsatisfactory growth and development requires even more complete examination, including basal metabolism, blood chemistry, and roentgenologic studies, on the one hand, and, on the other, thorough inquiry into the circumstances of family and school. The importance of a systematic program of investigation cannot be overemphasized.

Suboptimal circumstances in family life may often be difficult to define or to establish, especially if economic and social backgrounds are quite acceptable. Most discerning inquiry may be required. The day's schedule from sun up to sun down and beyond must be inquired into for the purpose of establishing habitual traits which by themselves would be harmless but which, acting together, might produce a combined effect that could no longer be neglected. Stability and good management of a home cannot always be judged on outward appearances; moreover, circumstances that are apparently satisfactory may nevertheless not be so.

The acid test for a subject who fails to respond to ordinary or obvious measures and whose family history shows little at fault after careful inquiry and observation is to place the child in a controlled environment that is suitable to all concerned. Such a procedure will soon demonstrate whether the failure to make up developmental lag is destined to be a simple or a difficult matter, and hence whether all the previous circumstances of a child's life were actually as good as they originally appeared to be. A description of the general improvement that may be expected under such management in cases of simple malnutrition is given in another paper[10] of this series, along with the after-history of T. B.

At this point it is necessary only to re-emphasize the comparatively great significance that further examinations are found to have when these have been instigated for the direct purpose of correlating Grid evidence of objectionable growth and development with environmental stimuli in a child's life. In the vast majority of cases poor environment and defective growth will be associated as cause and effect; in relatively few instances, where neither disease nor environment can be held to account, will there be need to fall back on or to investigate the more remote properties of constitution and heredity. Many children of Southern European parentage, for example, show a tendency to develop on auxodromes in and about the 82 per cent standard. This would, of course, be good cause for initial inquiry, but it should be ascribed to genetic influences only as long as the child remained on schedule. Departure from late schedules has, to be sure, the same significance and

calls for the same investigation of medical history and family circumstances as departures from any other schedule.

Finally, the urgent plea for guidance which is a main theme in group health work, such as in schools, can be more objectively carried out on the basis of an actual demonstration that growth and development are faltering or have already faltered. Cooperation between all concerned can be more reasonably expected and more intelligently established. From the administrative point of view, it will be possible to gauge the urgency of various cases and to concentrate attention where growth and development have been shown to be most seriously affected. A medical supervisory program for children, specifically organized to study, to measure, and systematically to follow up their growth and development, has a much more tangible end than one whose purpose is simply to check their health. In pursuing that end there is the assurance not only that concrete effects will often be recognized and therefore dealt with sooner than otherwise but also that improvement in growth and development cannot possibly escape improving health at the same time.

RÉSUMÉ OF PRINCIPLES AND METHOD

The first procedure in assessing the physical condition of children should be a systematic evaluation of their growth and development. Specifically, it is necessary to determine whether or not growth and development have been proceeding satisfactorily, and if not, in what respect and to what extent these fundamental processes are manifesting undesirable features.

All the essential information required for an objective appraisal of growth and development may be systematically obtained by reading a child's Grid record as plotted from routine heights and weights. The technique of appraisal has been reduced to two simple steps: (1) the evaluation of physical status at every given point and (2) the evaluation of physical progress from point to point.

Physical status is assessed in terms of physique, developmental level, and nutritional grade. It does not depend on age, which is concerned, instead, with physical progress.

The character of physical progress is ascertained from two kinds of evidence: (a) the curve of development traversing the channel system and (b) a child's own auxodrome.

The direction which (a) takes with respect to the channel system indicates whether changes in physique are or are not accompanying development, whereas (b) shows how long a child has taken to proceed from one level to another and, consequently, by comparison with the pattern of a neighboring standard auxodrome, whether that child is progressing on schedule or if not whether his development is being accelerated or retarded.

SUMMARY AND CONCLUSIONS

1. To illustrate both the principles and the method of Grid analysis, the case of a lad of 12½ years of age is reviewed in detail. His three-year progress toward malnutrition during the latter part of a five-year period of observation is clearly revealed and easily visualized in his Grid record. But this unfavorable trend of events was not suspected, and it was not recognized on the basis of periodic examination, routine history, or by other means. Moreover, although the Grid evidence of failing growth and development was conclusive, neither standard height-weight-age tables nor Tuxford's index succeeded in identifying the boy as in need of thorough check-up and remedial care.

2. There are two objective signs of ordinary malnutrition in the making that are characteristic: (1) developmental lag, or failure of a child to keep up with his expected schedule of progress, and (2) loss of physique, consequent on a shift in nutritional gradient away from the direction of the channel system toward its lower outer border.

3. The advent of lag is regularly the earlier sign which forewarns of oncoming malnutrition and it may even precede real evidence of a change in gradient by as much as six months or a year. But both lag and angular departure from a channel course can invariably be demonstrated from two to five years before the clinical picture of undernutrition becomes definite or sufficiently obvious to have a child referred for treatment.

4. These facts explain how a child, though still situated in channels where physical status deserves an over-all rating of "good," may nevertheless be undergoing profound changes which, for the time being, are evident only through lag in development and which, not until later, will cause a directional shift that inevitably leads, when it is sufficiently prolonged, to loss of physique.

5. The appearance of developmental lag is a sensitive, yet very definite sign that a child be placed under close observation. Monthly check-up will soon disclose whether lag is persisting or whether recovery is on the way. Meanwhile efforts should be made to correlate unsatisfactory growth and development with physical findings but also with environmental stimuli in a child's home and school life.

6. Specific retardation is the time equivalent of lag; it is essentially time lost which can be made up by overcoming lag. When this is accomplished, the child is back on his schedule of development.

7. The same phenomena that characterize the earliest stages of incipient undernutrition can also be demonstrated in a Grid record plotted from the recent (1941) data of Stuart and Kuhlmann on French children in Marseilles.

8. In the matter of prognosis it may prove even more significant at times to show that growth and development have been satisfactory than to detect unsatisfactory progress. But, while a child's keeping to his

channel and to his schedule of development is definite evidence that growth and development are up to par, it must not be forgotten that certain major lesions and some minor physical defects may themselves never influence growth, nutrition, or development at all. Far outnumbering these subjects, however, are children everywhere in whom growth and development ebb and flow with the circumstances of their lives. For them, a continuous chart of growth and development provides the guidance that is sought.

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THE FAMILIES OF THE CHILD RESEARCH COUNCIL

A Study of Families Whose Children Are Similar to Those in Urban Pediatric Practice

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THE pediatrician may have wondered, during his years of practice, just what kind of a sampling of the general population his patients and their families represented as to education, occupation, income, size of family, and similar items. Very few physicians have been able, however, to make a systematic study of the families in their practice in order to obtain reliable information in the socio-economic sphere over a period of years because of the time consumed in doing so and the turnover in patients from time to time. The need for such information is apparent when one notes the increasing emphasis being placed on the understanding of the "whole child" rather than merely a specific illness. The Child Research Council, an independent research institute headed by a pediatrician and affiliated with the University of Colorado School of Medicine in Denver, is equipped to make such a study. This Council follows children in families which are similar in most respects to those found in the pediatrician's practice. Our series is composed of children coming from a diversity of families scattered up and down the social and economic scale. Although there are no extremes such as poverty-stricken parents or retired millionaires, yet we do find carpenters and engineers, clerks and lawyers, or leisurely housewives contrasted with career women among those present. The babies accepted for study are within normal healthy limits at the start of life, but in the group of growing children are to be found the same general run of children's diseases which the pediatrician encounters.

The Child Research Council is devoted to the study of children as they develop from birth into maturity. Its purpose is to set up more adequate standards for the appraisal of growth, development and health of the individual child. The physical, social, and mental make-up of each child has been taken into consideration in an effort to obtain an adequate picture of the child as a whole. An excellent example of the picture we are attempting to portray is given at staff conferences. At this time our pediatrician, psychologist, anthropometrist, social worker, and workers in the various medical sciences gather together to offer their contributions, which go to make up a vivid, accurafe account of the child as a living functioning organism.

The sociologic aspect of our study of the child represents an attempt to learn something about his social and environmental life. This type of research affords us an opportunity to see what kind of a home Jack

From the Child Research Council and the University of Colorado School of Medicine.

has, what his characteristics are in the way of jealousy, food likes and dislikes, what his teacher thinks of him, whether his family is larger or smaller than average, and whether he lives in a neighborhood where infant mortality is high. These factors in Jack's environment illustrate the sort of useful data being collected by the social worker, during her observations of the home, school, and community, and in her statistical study of the group as compared with the Denver population and with that of the United States.

The home of the child is studied by means of yearly visits. A question blank is used during the interview and the information obtained is then written up in diary form and placed in the child's record. During the first visit to the home the parent is asked questions about the environmental history, such as the education, occupation, and religion of the child's grandparents, the relationship between the child's mother and her family and many other pertinent facts. On all succeeding visits questions pertain to the present environment of the child. They include such subjects as a description of the house and its furnishings, recreational interests of parents and child, such as movies, radio programs, reading interests, etc., the maid and her relationship to the child, disciplinary measures practiced, the amount of allowance given the child and how he uses it, the sex education given the child, what kind of an adjustment he has made in school, religious training, and other topics of possible interest in relation to the understanding of the child. Occasionally, at staff conferences, other sidelights regarding the home and family are presented when the worker gives her own impressions in addition to the parent's statements. The Minnesota Home Status Index,[1a] a scale for measuring urban environment, is another source of information regarding the home. This scale was developed by Dr. Alice Leahy, Associate Professor of Sociology at the University of Minnesota, and is used to compare our group of families with those of the general population. The items included in the scale are: Children's Facilities, which covers questions regarding play equipment, lessons, camp and the like; Economic Status, which concerns itself with whether the family has an automobile, goes on a vacation yearly, has an electric refrigerator, and other modern conveniences; Cultural Status, which takes up the magazines read by parents, the professional clubs they belong to, whether they play musical instruments or have other special skills or cultural interests; Sociality Status, which includes sports, fraternities, social clubs, etc.; Occupational Status, which reveals what occupational group the father is in; and Educational Status, which is concerned with the amount of education the parents have received. The occupational index used in this scale is Goodenough and Anderson's classification of occupations[2] based on the U. S. Census Bureau figures, the Taussig classification of noncompeting occupational groups, and the Barr Scale of occupations which classifies them according to the demands made on mental ability.[1b]

The occupational groups are: professional, semiprofessional, skilled, semiskilled, slightly skilled, and day labor. A list of occupations is given with each classification.

The school is visited once a year at which time information is obtained from the teacher in regard to the child's adjustment, socially and academically. Such questions as these are asked: In what subjects does the child do his best work? Does he cause a disturbance in the classroom frequently? Does he daydream during class? Does he put forth effort in his work? This material is jotted down on a question blank, to be incorporated, later, in the child's diary record.

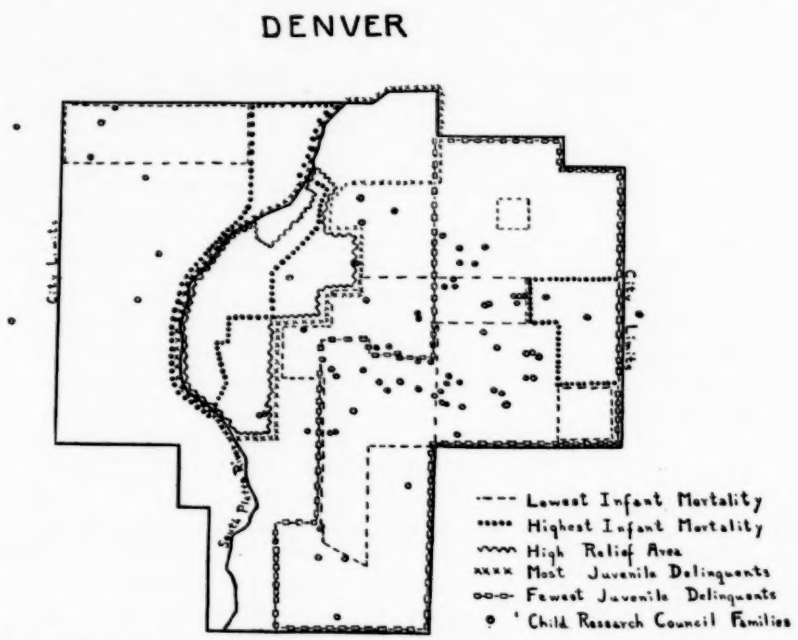

Fig. 1.—Map of Denver showing where our families are located in relation to high and low mortality, high and low delinquency, and high relief area.

The community has been studied by means of a zoning map,[3a] on which our families' residences have been plotted (Fig. 1). The map has been marked off into highest and lowest delinquency areas,[4a] highest and lowest infant mortality,[5] highest relief areas,[6] and desirable and undesirable building zones. Thus we are able to see whether Jack lives in a "good" neighborhood defined as one in which there are few delinquents, with few people on relief and a building zone regulation allowing only single dwellings and no hotels.

The data obtained from this study of the child and his family in the Child Research Council group are being compared with available data concerning the Denver population and that of the country at large.

TABLE I

YEARLY INCOMES OF CHILD RESEARCH COUNCIL FAMILIES AS COMPARED WITH THE INCOMES OF THE DENVER POPULATION

INCOME ($)	CHILD RESEARCH COUNCIL (%)	DENVER* (%)	GENERAL POPULATION† (%)
Over 50,000		Less than 1	Less than 1
20,000 to 50,000		1	1
10,000 to 20,000	5	3	3
5,000 to 10,000	19	10	8
2,500 to 5,000	47	35	32
1,000 to 2,500	28	45	49
Under 1,000	1	5	6

*Reference 7 (a).
†Reference 7 (b).

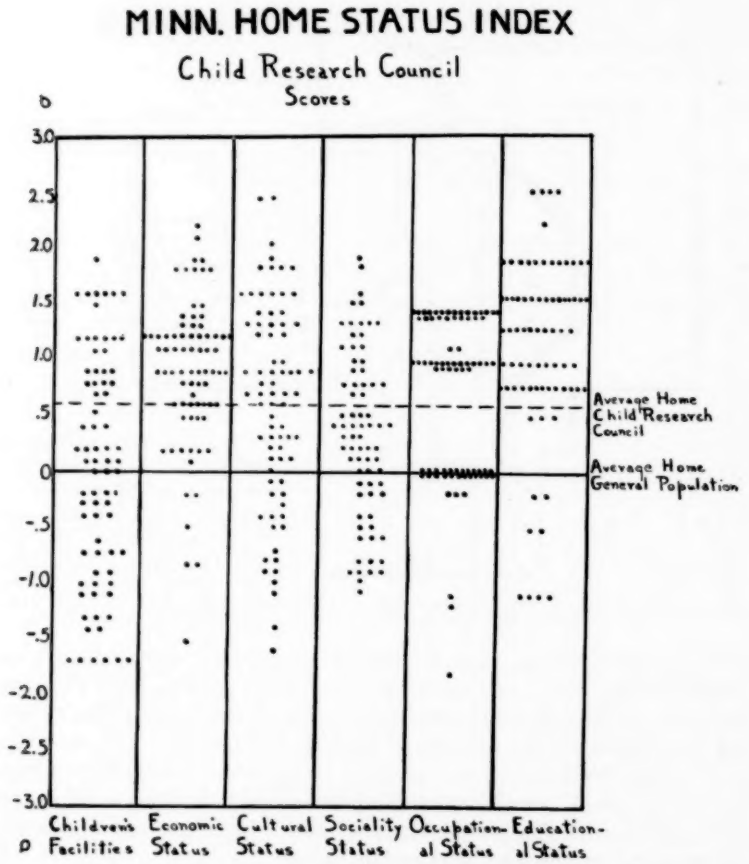

Fig. 2.—Comparison between Child Research Council families and those in the general population as shown by the Minnesota Home Status Index. The scale at the left is based on the accepted system of scoring in this index, each unit representing one sigma. The broken line indicates the average of total scores on Child Research Council families.

The following is a presentation of some of our findings on education, occupation, income, size of family, race, religion, and related facts.

There are now 115 children in the Child Research Council series, coming from eighty-four homes. Of these homes, only 5 per cent are located in Denver's relief area or in its high delinquency area, while 65 per cent are located in the area of fewest delinquents. In the high infant mortality area we find only 6 per cent of our families, in the low infant mortality area 37 per cent, and in those areas between high and low, 57 per cent (Fig. 1).

The majority of our families live in desirable residential areas of Denver as is shown by the study made on the location of homes in relation to building zones. Eighty-two per cent are living in A or B zones, which are those building zones having the highest requirements from the standpoint of "health, welfare, morals, and safety of the people."[3b] Seven per cent are living in D or E zones, which have the lowest building requirements. Six per cent live outside the city limits in small towns.

All but five of our families answered the questionnaire on salaries. The average incomes of our group are above the average of Denver and the general population. We have no families receiving salaries over $20,000 yearly, while Denver and the United States have a few in the $50,000 class and over. Almost half of our group fall within the $2,500 to $5,000 class. We find 35 per cent of the Denver population and 32 per cent of the general population in this bracket as is shown in Table I.

TABLE II

ITEMS IN MINNESOTA HOME STATUS INDEX	PER CENT OF CHILD RESEARCH COUNCIL FAMILIES WHO ARE ABOVE AVERAGE OF GENERAL POPULATION
Children Facilities	51
Economic Status	92
Cultural Status	75
Sociality Status	64
Occupational Status	63
Educational Status	88

The Child Research Council families are found to be above the average of the general population living in an urban environment according to ratings made on the Minnesota Home Status Index. Our homes rate highest on Economic Status and lowest on Children's Facilities. However, a comparison of our scores with those of the general population shows that we are above the average of the population in all classifications included in the index, as is shown in Table II.

The scores in each item and the total scores of Child Research Council families are shown in Figs. 2 and 3.

Half of our families have no paid assistance, 39 per cent have full-time maids, and 11 per cent have part-time help for housekeeping or

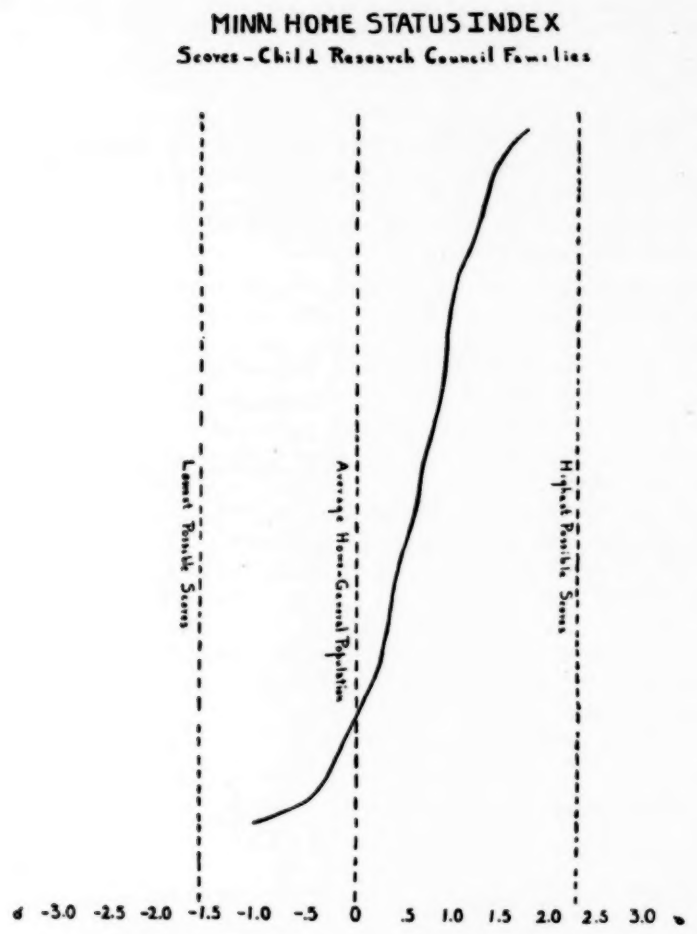
MINN. HOME STATUS INDEX
Scores - Child Research Council Families
Lowest Possible Scores
Average Home-General Population
Highest Possible Scores
-3.0 -2.5 -2.0 -1.5 -1.0 -.5 0 .5 1.0 1.5 2.0 2.5 3.0

Fig. 3.—The range of scores of Child Research Council families on the Minnesota Home Status Index.

care of children. Fourteen per cent of our families are listed in Denver's Social Record,[8] which lists those citizens of Denver who have been chosen as being prominent in business or socially. These families are not all rated high on the Minnesota Home Status Index but are scattered from high to low on the score range. One family is listed in Who's Who in America, 1940-41.[9] One in 4,300 of the general population is listed in Who's Who in America.[10] Eighteen per cent of our mothers are members of Junior League.

Our families were found to be in the high occupational levels according to Goodenough's and Anderson's classification of occupational groups. Over half of our fathers are engaged in professional or semi-

professional groups, and only 4 per cent are employed in unskilled labor or day labor. The occupational group as compared with the general population is shown in Table III.

TABLE III

OCCUPATIONAL GROUP	CHILD RESEARCH COUNCIL (%)	GENERAL POPULATION* (%)
Professional	32	4
Semiprofessional	26	10
Skilled	34	22
Slightly skilled	4	22
Unskilled	3	8
Day labor	1	13

*Reference 1 (c).

We have one family on relief and the rest are self-supporting. Ten per cent of our mothers are working full time. Of married women in Denver, 17 per cent were in occupations during 1930.[11c] All the Child Research Council youths between 16 and 21 years of age (nine boys and one girl) are in school with one exception, and 80 per cent of them are doing part-time work after school hours. Of all Denver youths, 16 to 21 years of age, 44 per cent are in school, 20 per cent are employed full time, and 8 per cent are working part time, not attending school.[4]

TABLE IV

EDUCATION OF CHILD RESEARCH COUNCIL PARENTS AS COMPARED WITH THE DENVER POPULATION

EDUCATIONAL GROUPS	CHILD RESEARCH COUNCIL		DENVER*	
	FREQUENCY %	CUMULATIVE FREQUENCY %	FREQUENCY %	CUMULATIVE FREQUENCY %
Completed college	43	43	8	8
Entered college	19	62	9	17
Finished high school	24	86	24	41
Entered high school	6	92	16	57
Eighth grade	8	100	42	99
Not reported	0	0	1	1

*U. S. Census Bureau, 1940.

Our parents are well educated, as is indicated by the figures in Table IV. Forty-three per cent of our fathers and mothers have either finished college and stopped there or have taken graduate work in addition to college. Eight per cent of the Denver population completed college.[12a] (Figures for the general population are not yet available.) Eight per cent of our parents finished the eighth grade only, while 42 per cent of the Denver population have gone through the eighth grade and stopped there.

Our fathers and mothers have had almost equal amounts of education, except that 30 per cent of our fathers have had postgraduate work above college level while only 11 per cent of the mothers have had this amount. Forty-four per cent of our fathers have completed

college or taken postgraduate work in addition, and 43 per cent of our mothers fall within this group (Table V).

Of the eighteen children of preschool age in the Child Research Council, eleven are attending preschools. One child attends public preschool, and ten are attending private preschools.

TABLE V

EDUCATION OF THE FATHERS AND MOTHERS OF THE CHILD RESEARCH COUNCIL

EDUCATIONAL GROUPS	FATHER		MOTHER	
	FREQUENCY %	CUMULATIVE FREQUENCY %	FREQUENCY %	CUMULATIVE FREQUENCY %
Graduate	30	30	11	11
Completed college	14	44	32	43
Entered college	20	64	19	62
Finished high school	22	86	26	88
Entered high school	5	91	5	93
Eighth grade	9	100	7	100

Child Research Council families are only slightly smaller than those of Denver and the general population. The size of our families as compared with those of Denver and the general population are shown in Table VI.

TABLE VI

SIZE OF FAMILY	CHILD RESEARCH COUNCIL (%)	DENVER POPULATION* (%)	GENERAL POPULATION† (%)
3	35 (1 child)	42	30
4	49 (2 children)	29	27
5	13 (3 children)	14	17
6	2 (4 children)	8	11
7	0	4	7
8	0	2	5
9	0	1	2
10	1 (6 children)		1
11	0	Less than 1	Less than 1
11	0		

*Reference 11 (b).
†Reference 11 (a).

We have one adopted child in our series and one pair of twins. Of our mothers, three have been divorced and two of the three have been remarried.

Our records show that 95 per cent of our parents are native born, while 5 per cent are foreign born. We have no Negroes in our series. Of the Denver population, we find that 77 per cent of the families are native-born white, 18 per cent are foreign born, 3 per cent are Negroes, and 2 per cent others[11b] (Fig. 4).

Over half of our families are Protestant, 9 per cent Jewish, 7 per cent Catholic, and 5 per cent mixed (one parent Catholic and one Protestant). The figures for Denver and the United States are not as high for Protestants. Religious groups of the Child Research Council as compared with those of Denver and the general population are shown in Table VII.

TABLE VII

RELIGIOUS GROUP	CHILD RESEARCH COUNCIL (%)	DENVER* (%)	GENERAL POPULATION† (%)
Protestant	79	50	69
Roman Catholic	7	35	24
Mixed	5	–	–
Jewish	9	14	6
Others	0	Less than 1	Less than 1

*Reference 13 (a).
†Reference 13 (b).

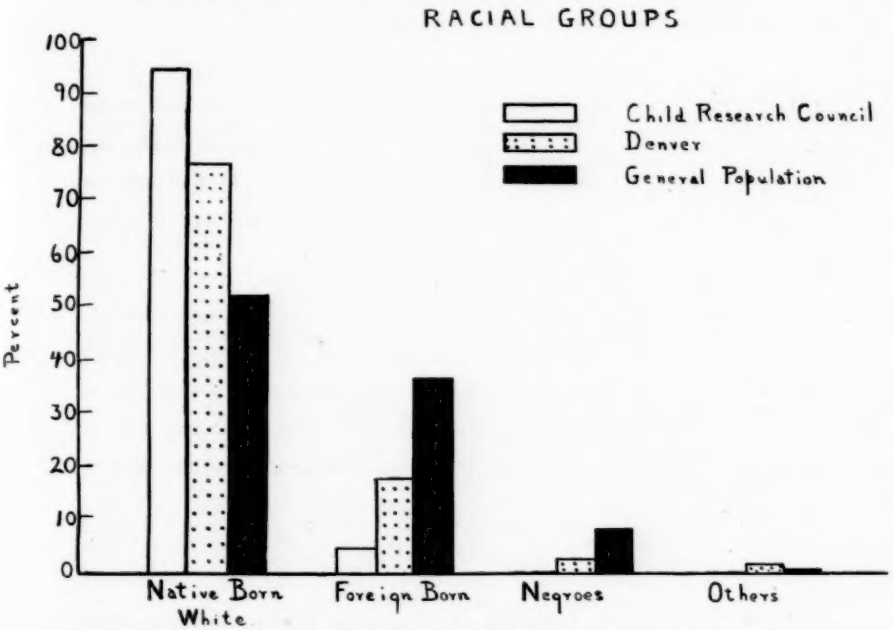

Fig. 4.—Racial groups of the Child Research Council as compared with Denver and the general population.

There are more Jews and Catholics in Denver than there are in the general population.

SUMMARY

A majority of Child Research Council families are living outside of the undesirable areas of the city as revealed by relief reports, delinquency records, infant mortality rates, and building zone regulations.

Our families are well above average for Denver or for the general population of the country in income levels, in per cent of native-born parents, and in the following items as scored on the Minnesota Home Index scale: occupational status, education, social and cultural status in the community.

In size of family and in facilities for the children, they are near the average for the community.

Although there are individual differences in practice, or in the city in which a given pediatrician may be working, he may find in this study a base line from which to start. It is hoped that the data presented may be of some value as well to the general practitioner and other professional people treating or studying a series similar to ours. It is also to be hoped that this brief cross-sectional type of analysis may stimulate others to study these social and economic factors throughout the growth span of the child. Such information is essential if we are to understand individuals well enough to appraise adequately the problems they so often present.

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Erratum

On page 741 of the December, 1942, issue of the JOURNAL, the article entitled "The Treatment of Ichthyosis With Vitamin A" by Howard G. Rapaport, M.D., Harold Herman, M.D., and Edward Lehman, M.D., the *A* and *B* parts of Fig. 4 are reversed. *B* should be *A* and *A* should be *B*.

The Pediatrician and the War

AGE AS A FACTOR IN SUSCEPTIBILITY OF YOUNG WORKERS TO TOXIC SUBSTANCES

WILLIAM M. SCHMIDT, M.D.
WASHINGTON, D. C.

IN A period of war such as this, the employment of boys and girls increases very rapidly, and many young persons enter occupations which ordinarily are filled by adult workers. Employment certificates in 1941 showed an increase of 100 per cent over the preceding year, and, perhaps more important, indicated that boys and girls 16 and 17 years of age were entering a variety of manufacturing jobs in which formerly there had been small employment among this age group.

Protection of these young workers is accepted as a responsibility of government, and in the present war increased efforts in this direction are especially necessary. When 16- and 17-year-old boys and girls enter employment today, it is especially important that they be protected from injury and directed into employment where their skills may be developed and most effectively used.

The general minimum age for employment established by the Fair Labor Standards Act of 1938 is 16 years, and a minimum age of 18 years is provided for occupations "found and declared" by the Chief of the Children's Bureau to be particularly hazardous or detrimental to the health or well-being of persons 16 to 18 years of age. In the determination of occupations particularly hazardous or detrimental to health, the Children's Bureau has followed two general principles: (1) That occupations particularly hazardous for adults are also particularly hazardous for minors and (2) that certain occupations in which adults may work with reasonable safety may in fact be particularly hazardous or detrimental to the health of young workers.

The first principle especially has been followed in the orders already issued under the Act. In these orders, establishing a minimum age of 18 years for certain occupations characterized by an outstanding accident hazard, the Children's Bureau has recognized that, in spite of the progress that has been made in safeguarding workers and in accident prevention, certain occupations are still hazardous to persons of all ages, including minors.

Great progress also has been made in the application of medical and engineering measures for the control of industrial exposure to toxic substances. The adequacy of such control may be evaluated by means of periodic medical examination of employees and frequent quantitative determinations of the concentrations of toxic substances in the atmosphere of the workrooms, compared to maximum permissible concentrations, which have been established and widely accepted for a number of toxic substances. It must be recognized, however, that medical and engineering control measures are by no means universally employed,

From the Industrial Division, Children's Bureau, U. S. Department of Labor, Washington, D. C.

and as yet many workers are without the protection that these measures afford. Therefore, in the absence of such control, a potentially hazardous situation may well exist for employees, and sound policy requires that minors should be protected from such exposure.

The second principle guiding the Children's Bureau in its determination of occupations hazardous to the health of minors gives rise to the question of the relative susceptibility of immature individuals to industrial poisons. There is little direct evidence on this question, for, in the main, minors under 18 years of age have not been employed in large numbers in occupations involving well-defined exposure to toxic substances. During periods of rapidly expanding employment and relative labor shortage, however, the employment of minors increases very rapidly, and placements of young persons may be made with little thought of potential health hazards. For example, during World War I, many young persons were employed in the manufacture of explosives and in the painting of self-luminous (radium) dials, occupations which are now prohibited for persons under 18 years by orders issued under the Fair Labor Standards Act. Lacking conclusive direct evidence on the question of the relative susceptibility of immature individuals, it seems desirable to review some of the evidence indirectly bearing upon the problem.

RESPIRATION

Immature persons breathe a greater volume of air per unit of time per unit of body weight, both at rest and during exercise, than do adults. This results from the greater basal metabolic rate in immature persons per unit of surface area, and a greater surface area per unit of body weight. Consequently at any given atmospheric concentration of a toxic gas, immature persons will attain a given percentage of saturation of the blood and body tissues at a more rapid rate than will adults.

The pulmonary ventilation found in a small number of presumably healthy youths and young adults, as reported by Robinson,[1] is shown in Table I.

TABLE I

PULMONARY VENTILATION OF SUBJECTS AT REST

NUMBER OF SUBJECTS	AGE (YR.)	C.C. OF AIR BREATHED PER KILOGRAM PER MINUTE	
		MEAN	EXTREMES
11	13 to 15	132	106 to 169
12	16 to 19	109	78 to 152
10	20 to 29	93	76 to 108

The lowest value observed for the youngest age group in the table is approximately equal to the highest value observed in the oldest age group, while the pulmonary ventilation of the age group 16 to 19 years was intermediate. It would be desirable to have data of the same nature by single years of age and with estimates of developmental status.

The greater pulmonary ventilation in adolescents does not necessarily lead to a higher blood concentration of toxic substances. If a given concentration is attained in a shorter time, however, it may be of importance under conditions leading to acute intoxication, for younger individuals might succumb before older ones have been appreciably affected. Whether or not a more rapid rate of absorption would be of importance under conditions leading to chronic intoxication would be at least partly dependent upon the mechanism of excretion and detoxification.

CIRCULATION

According to Henderson and Haggard[2] the rate of absorption of a toxic gas, present in given concentration in the atmosphere, is influenced not only by the pulmonary ventilation, but also by the circulation. The greater the amount of blood flowing through the lungs in one minute, the more rapid the rate of absorption of a toxic gas present in the atmosphere.

The cardiac output per square meter of body surface in a group of fifty normal young adults has been found to have an average value of 2.2 L. per minute.[3] Even if this value were the same in adolescents as in adults, a greater volume of blood per kilogram of body weight would circulate per minute in the adolescents. However, the little information available indicates that the cardiac output per square meter is somewhat greater in younger persons, probably about 2.5 in children, as compared to 2.2 in young adults and 2.0 in older ones, and therefore their cardiac output would be even greater in proportion to their body weight.[3]

DETOXIFICATION

Animal experimental evidence, supported by a limited number of observations in man, leads to the conclusion that the mechanism of detoxification of some toxic compounds is relatively less effective in the growing individual than in the fully grown, and that, therefore, a greater hazard results from exposure to such industrial poisons as benzene, monohalogenated benzenes, pyridine, naphthalene, and others for an immature person than for a mature one.

In animal experimentation it has been found that the very young animal is unable to detoxificate as large an amount of toxic carbocyclic compounds as is the adult animal. For example, Stekol showed marked differences in detoxification of single doses of bromobenzene in growing and in adult dogs. The observations on one animal at 6 weeks and at 38 weeks of age, shown in Table II, are representative of the results.[4]

TABLE II

DETOXIFICATION OF BROMOBENZENE IN DOGS AT 6 AND 38 WEEKS OF AGE

	WEIGHT (KG.)	DOSE OF BROMOBENZENE (MG.)	PER CENT OF DOSE DETOXIFICATED
Dog 25 at 6 weeks of age	1.6	300	30.2
Dog 25 at 38 weeks of age	8.4	300	82.5

The wide difference in percentages given in Table II marks, of course, the difference between a very young animal and one fairly well advanced in development. It is dependent upon the greater mass of tissue in the older animal, which permits detoxification of a correspondingly greater dose of the toxic substance. In human beings 16 or 17 years of age as compared to older persons one would expect the difference to be considerably smaller. Individuals 18 years of age and older, as a group, weigh more than those 16 and 17 and would therefore be able to metabolize a larger dose of such toxic substances as bromobenzene.

The mechanism of detoxification of these substances involves the withdrawal from the body tissue of sulfur-containing amino acids, essential for growth. In a study of rats, White and White found that unless the

growing animal received a diet that was abundant in these essential growth-promoting substances, there was an inhibition or complete cessation of growth.[5] Even though the diet of the growing animal may be such that ample amounts of all the dietary components, including the organic sulfur (cystine and methionine) are available to meet the need for growth and detoxification, the continuous breakdown caused by the invading substances and the subsequent repair of the damaged tissue cannot be considered a harmless process in the growing organism.[6]

The involvement of other nutritionally essential substances, for example, vitamin C, during chronic exposure to benzene and its derivatives, has been demonstrated, and thus an additional effect of the absorption of many toxic substances may be to deprive the growing organism of a proportion of otherwise available vitamin.[7]

GROWTH

Impairment of the growth of animals may result from the absorption of other types of toxic substances. Among them are lead,[8] selenium compounds,[9] and carbon monoxide,[10] in addition to the carbocyclic compounds discussed in the previous section. It is clear that if a toxic substance, in addition to its other harmful effects, retards or completely inhibits growth, greater damage has occurred, whatever the mechanism of this action, than would occur from a similar degree of intoxication in an individual whose growth has already been completed.

If it were possible to proceed on the basis of biologic principles, placements of young persons in occupations with potential exposure to substances that may interfere with growth would be made only after an individual appraisal of each candidate's maturity. After appraisal, placement could be made of those persons whose period of growth had been completed. An arrangement administratively more expedient, however, is to establish a minimum age for such employment, which, while not equally suitable for all individuals, provides proper protection for the greatest number. Sixteen years is now widely established as a minimum age for factory employment, but at this age growth is rarely completed in boys, and even among girls many individuals continue to grow in stature, and most in weight. In most individuals of both sexes, skeletal development is not substantially completed before the age of 18 years. At 20 years of age, however, most individuals have completed growth or have very nearly attained complete growth. In the absence of individual appraisal, therefore, the age of 18 years appears to be a reasonable minimum age for employment in occupations in which there is potential exposure to toxic substances.

JUDGMENT AND PRUDENCE OF WORKERS

Habits of work and those factors of judgment, prudence, and insight which may rest upon experience are not often likely to be developed in a 16-year-old boy or girl to the extent necessary for him to exercise reasonable caution and to conduct himself safely. Many industrial processes require the use, from time to time, if not constantly, of respirators or other personal protective apparatus. A young person lacking in sufficient judgment and prudence may be inclined to neglect the use of such devices. Curiosity and lack of caution may lead a younger worker to commit foolish and negligent acts and to expose himself unnecessarily even against advice.

SUMMARY AND CONCLUSION

Experimental evidence indicates that growing animals—and there is sound reason to believe growing boys and girls—because of physiologic factors are more susceptible to injury from industrial poisons than adults. Lack of mature judgment renders young persons more likely to neglect the use of personal protective measures and observance of other necessary safe practices.

Prudence in the conservation of the labor force as well as protection of young persons requires the selection of mature individuals for work in occupations where exposures to toxic substances occur. Persons under 18 years of age entering employment should be excluded from occupations in which there is exposure to toxic substances, even though control measures considered reasonably adequate for adults are in operation, and should rather be placed in occupations essentially free from such exposures.

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American Academy of Pediatrics

Proceedings

Report of the Meeting of the Executive Board of the American Academy of Pediatrics

Chicago, Ill., Nov. 3, 1942

A meeting of the Executive Board of the American Academy of Pediatrics was held at the Palmer House, Chicago, on Tuesday, November 3, 1942, with the Vice-President, Dr. Borden S. Veeder, in the Chair.

The Chair announced that he had received a letter from Dr. E. C. Mitchell regretting his inability to attend the Board meeting because of illness.

The following applications submitted by the Regional Committees were approved:

Region I

Dr. Beatrice Bergman, New York City, N. Y.
Dr. Otto E. Billo, Bronxville, N. Y.
Dr. Milton J. H. Grand, Bronx, N. Y.
Dr. Samuel B. Grimes, Baltimore, Md.
Dr. Walter Harris, Forest Hills, N. Y.
Dr. Marion Hotopp, Dover, Del.
Dr. William B. Nevius, East Orange, N. J.
Dr. Emelie M. Perkins, Rutland, Vt.
Dr. Rudolf L. Roddy, Abington, Pa.
Dr. Eugene B. Schuster, Pittsburgh, Pa.
Dr. Leslie N. Silverthorne, Toronto, Ontario, Can.
Dr. Maxwell Stillerman, Great Neck, L. I., N. Y.
Dr. Edward J. Thalheimer, Vineland, N. J.
Dr. Vincent Tosti, Ridgewood, Queens, N. Y.
Dr. M. L. Weimann, Haddon Heights, N. J.
Dr. Carl Zelson, New York City, N. Y.
Dr. Bernard Zuger, Brooklyn, N. Y.

Region II

Dr. Ruth R. Berrey, Birmingham, Ala.
Dr. Roger W. Dickson, Atlanta, Ga.
Dr. Wallace Sako, New Orleans, La.
Dr. Joseph M. Sloan, Corpus Christie, Texas.

Region III

Dr. Arthur E. Karlstrom, Minneapolis, Minn.
Dr. George C. Kimmel, Red Wing, Minn.
Dr. M. I. Saberman, Chicago, Ill.
Dr. Arthur H. Spreen, Cincinnati, Ohio.

Region IV

Dr. S. Gorham Babson, Portland, Ore.
Dr. Rea F. Chittenden, North Hollywood, Calif.
Dr. Joseph H. Davis, San Francisco, Calif.
Dr. Robert S. McKean, Boise, Idaho.
Dr. Ina M. Richter, Santa Barbara, Calif.
Dr. George H. Schade, San Francisco, Calif.
Dr. Walter P. Sherrill, Phoenix, Ariz.
Dr. James R. Sickler, Tucson, Ariz.

The following members were placed on the Emeritus list:

Dr. R. S. Friedley, Akron, Ohio.
Dr. Lawrence T. Royster, Charlottesville, Va.
Dr. Archibald D. Smith, Brooklyn, N. Y.
Dr. L. J. Osborne, Owego, N. Y.
Dr. J. H. McKee, Philadelphia, Pa.

The Report of the Treasurer was accepted.

It was moved, seconded, and carried that there be no annual meeting held in 1943 and that regional meetings not be held for the present.

It was moved, seconded and carried that a meeting of the state chairmen shall be called when, as and if it seems advisable, at the discretion of the Executive Board or of the Regional Chairman. It was suggested that local state meetings be encouraged for the purpose of maintaining and continuing child health efforts in war time.

It was moved and carried that the employment of the Director of Public Relations be discontinued for a period of one year.

The question of visitors at the annual meeting was discussed. It was moved, seconded, and carried that interns, other house officers and nurses, with the rank of supervisor or higher, shall be the only visitors admitted without the payment of a registration fee, except those that are recommended by members of the Executive Board.

The scientific exhibits were discussed. It was moved and carried that the Treasurer be given the power to reimburse out-of-pocket expense for exhibits for any amount that seems reasonable and that any extraordinary amount shall be referred to the Executive Board for action.

Dr. Martmer stated that the food industry is faced with the problem that the War Production Board had called a meeting in Washington for November 4 to decide whether the manufacture of the so-called puréed foods shall be continued or discontinued. On motion duly made and seconded, it was voted that the following telegram be sent to the War Production Board:

"The Executive Committee of the American Academy of Pediatrics, representing 1,500 children's doctors in America, in session Nov. 3, 1942, urge that every effort be made to maintain the supply of infants' foods, particularly puréed vegetables and fruits, and meat soups; that under present conditions these articles represent the most valuable supply of food of this nature that could be produced, that the maintenance of this supply is essential to the nutrition of the children of America, and its use will eliminate waste in the home."

A letter was received from Dr. L. K. Frank concerning the drafting of 18- and 19-year-old boys. It was moved, seconded, and carried that no recommendation be made inasmuch as this age group is beyond the province of the Academy.

Dr. George M. Wheatley of the Metropolitan Life Insurance Company presented a proposed pamphlet on rheumatic fever to be gotten out by this Company and

asked the approval of the Academy. It was moved, seconded, and carried that a special committee, consisting of Dr. Alexander T. Martin, Chairman, Dr. Hugh McCulloch, and Dr. Stanley Gibson, be appointed with power to act in approving the pamphlet on rheumatic heart disease to be issued by the Metropolitan Life Insurance Company. A mimeographed letter prepared by Dr. Martin shall be sent out to all members of the Academy and the arrangements for sending it out shall be settled between Dr. Wheatley and the Secretary-Treasurer.

It was moved, seconded and carried that the release on rheumatic fever and rheumatic heart disease be given to the press (November 4).

A letter regarding iodized salt in the prevention of goiters, under the supervision of the American Public Health Association, was read. It was decided that the Academy should concur in the action to continue the use of iodized salt for the prevention of goiters in those areas where it is necessary, and the matter should be referred to the Committee on Nutrition for their reaction.

It was moved, seconded, and carried that the Committee on Medical Education, comprising all three groups, take up for discussion this matter of providing courses in pediatrics in different parts of the country after the war for instruction of members who had been in service, with instructions to report back to the Executive Board as to how it can best be handled.

The cooperation of the Academy was offered to the American Legion in its child health program, and a committee was appointed in June to approve material on nutrition which was to be put on a sound-slide film. Mr. Waters presented the sound recording. After listening to the first two recordings covering the introduction to the program which was not approved by the Board, it was moved, seconded, and carried that the President and Secretary be requested to interview the American Legion authorities and discuss the whole proposition.

It was moved, seconded, and carried that Dr. Edward C. Mitchell be made chief liaison officer and Dr. Lawrence F. Richdorf be made associate liaison officer between the American Legion and the Academy.

The report of the Committee on School Health was considered. It was moved, seconded, and carried that it is the opinion of the Executive Board that every possible means should be entered into for the widespread distribution of the pamphlet, "Medical Standards for Physicians in Schools." The Report of the Committee was adopted.

It was moved, seconded, and carried that the Board adopt the professional qualifications for administrative and full- or part-time staff physicians in school health services set forth in the report of the Committee on School Health for 1942 on Medical Standards for Physicians in Schools and that these be sent as far as possible to all educational authorities in the United States.

It was moved, seconded, and carried that these standards of professional qualifications be recommended by the Academy for all types of child health services to all national, state, and local governmental and nongovernmental agencies interested in any type of child health services for their guidance as to the future selection of the best professionally qualified physicians for all types of child health services.

The Report of the Committee on Library and Museum was presented and approved with four additional recommendations. It was moved, seconded, and carried that the Committee be empowered to accept funds and gifts under the conditions set forth in the report; that the amount of two hundred and fifty dollars be allocated for the promotion of this project.

The Reports of the following Committees were accepted and approved:

Committee on Camps
Committee on Contact Infections
Committee on Cooperation With Nonmedical Groups

Committee on Mental Health
Committee on Nursing Education
Committee on National Defense

Dr. Helmholz gave his report on the Committee on Pan-American Scholarships. It was suggested that the Committee be continued in an advisory capacity and that as soon as possible the additional administrative work be carried on by personnel attached to the central office. A report was also given at the same time on the Latin-American Fellowships and in this respect the sum of fifteen hundred dollars was allocated for the furthering of the Latin-American Fellowships and the additional administrative assistance required as additional scholarships had to be taken care of in the near future. The Executive Board approved the two plans which are to be submitted to the Latin-American Fellows: (1) Abstracts of the original articles in English, or Spanish, of THE JOURNAL OF PEDIATRICS and the *American Journal of Diseases of Children* for five dollars a year, and (2) a subscription of THE JOURNAL OF PEDIATRICS and abstracts of the original articles of the *American Journal of Diseases of Children* in English for ten dollars a year. The changes in the By-Laws for the Latin-American Fellows were discussed at length, and the following applications approved:

Alfonso G. Alarcón
Rigoberto Aguilar Pico
Alejandro Aguirre Torres
Enrigue Baz-Dresch
Hermilo Lamberto Castañeda
Federico Gómez Santos
Demófilo Gonzales C.
Carlos Herrera R.
Forrando Lopez Clares
Jesus Lozoya S.
Ismael Martinez Sotomayor
Jorge Munoz Turnbull
Augustin Navarro Hidalgo
Roberto L. Sanchez

Rafael Soto Allande

Owing to the fact that we are developing active Fellowship in the Latin-American countries, it was decided to temporarily postpone the recommendations of the Committee on Honorary Fellowships.

News and Notes

The next examinations by the American Board of Pediatrics will be given in St. Louis on March 27 and 28, 1943, and in New York on April 24 and 25, 1943.

Applications should be made to the Secretary, Dr. C. A. Aldrich, 707 Fullerton Avenue, Chicago, Ill., as early as possible.

Notice is hereby given that on and after July 1, 1943, candidates will no longer be accepted in Group I. This applies to physicians who have specialized in pediatrics for ten years or more. After that date all applicants will be placed in the same category.

The Executive Board of the American Academy of Pediatrics has authorized the establishment of a pediatric library and museum and a committee has been appointed to draw up plans. Under proper authority, the Jacobi Fund of the Section on Pediatrics of the American Medical Association will be transferred to the library and museum, if and when it is established. The Academy plans to make this a part of its activities and will transfer all its permanent historical records and other material now and in the future to the library. Following this, it is hoped that other material from outside sources will be drawn to this central repository.

The Committee* has had several meetings and plans in detail are being drawn up. The Committee appeals to the membership at large and any other interested individuals to send in comments, suggestions, and information that will be of help. It is hoped that information leading to the acquisition of material will be sent in promptly so that no collection or item will be lost to the pediatric public. Communications should be addressed to a member of the Committee:

Dr. Albert D. Kaiser, 16 N. Goodman St., Rochester, N. Y.
Dr. Ernest Caulfield, 683 Asylum Avenue, Hartford, Conn.
Dr. Hugh McCulloch, 325 N. Euclid Ave., St. Louis, Mo.

The following applicants were certified by the American Board of Pediatrics at the examination in Chicago, Nov. 1, 2, and 3, 1942:

Dr. John Milton Adams, 1009 Nicollet Ave., Minneapolis, Minn.
Dr. J. Roberto Aguayo, Caguas, Puerto Rico (At Children's Memorial Hospital, 707 W. Fullerton, Chicago, until Jan. 1, 1943)
Dr. Julius Aronow, 3460 Lawrence Ave., Chicago, Ill.
Dr. J. E. Bacon, 1200 Main St., Dubuque, Iowa
Dr. J. Joseph Baratz, 2735 Devon Ave., Chicago, Ill.
Dr. James Frazier Binns, 706 Church St., Nashville, Tenn. (in the Army)
Dr. Lawrence Breslow, 104 S. Michigan Ave., Chicago, Ill. (in the Army)
Dr. Edward William Bulley, Vicksburg Hospital, Vicksburg, Miss.
Dr. M. C. Carlisle, 1410 Austin Ave., Waco, Texas
Dr. Willie Mae Clifton, 645 Fullerton Parkway, Chicago, Ill.
Dr. Martha Eleanor Cook, Gordon Bldg., Lake Charles, La.
Dr. Jacob Adolph Danciger, 188 S. Bellevue, Memphis, Tenn. (in the Army)
Dr. William Deering, 1791 Howard St., Chicago, Ill. (in the Army)
Dr. Sol Paul Ditkowsky, Beech St., Normal, Ill. (in the Army)

*See Report of the Special Committee on Library and Museum of Pediatrics, J. PEDIAT. 21: 830, 1942.

Dr. James W. DuShane, 636 Church St., Evanston, Ill.
Dr. O. E. Ehrhardt, 107 S. 5th St., Springfield, Ill. (in the Army)
Dr. Lucas W. Empey, 106 Vernon St., Roseville, Calif.
Dr. Dorothy F. Falkenstein, 188 E. State St., Columbus, Ohio
Dr. Robert Raines Harriss, Hollywood Clinic, Hollywood, Fla.
Dr. Frank Dickerson Hazlett, 6 S. Main St., Washington, Pa. (in the Army)
Dr. Herbert Kahan, 45 Locust Ave., New Rochelle, N. Y. (in the Army)
Dr. Herschell Jerome Kaufman, Medical Bldg., Port Arthur, Texas (in the Army)
Dr. William White Kelton, Jr., 303 W. 15th St., Austin, Texas
Dr. Ernest R. Kimball, Jr., 1800 Wilson Ave., Chicago, Ill. (in the Army)
Dr. Joseph M. Klein, 219 S. Franklin St., Wilkes-Barre, Pa. (in the Army)
Dr. George John Klok, 532 First Ave., Council Bluffs, Iowa (in the Navy)
Dr. John Sanford Kruglick, 2800 Milwaukee Ave., Chicago, Ill. (in the Army)
Dr. Harry J. Lefkowitz, 10640 Carnegie Ave., Cleveland, Ohio (in the Army)
Dr. Edward Louis Levert, 3439 Prytania St., New Orleans, La.
Dr. Lavinia Gould MacKaye, 1715 S. University Ave., Ann Arbor, Mich.
Dr. Herman Braun Marks, 109 Broadway, Pawtucket, R. I. (in the Navy)
Dr. Eva Linn Meloan, Miss. State Board of Health, Jackson, Miss.
Dr. Betty Moody, 526 Richmond Road, Houston, Texas
Dr. William B. Mullins, 14 E. 9th St., Shawnee, Okla.
Dr. Richard Leedom Nelson, 1300 8th St., Wichita Falls, Texas
Dr. R. A. Norton, 740 St. Helen's St., Tacoma, Wash. (in armed forces)
Dr. Emanuel Padnos, 5944 Madison Ave., Chicago, Ill.
Dr. Ralph V. Platou, 1430 Tulane Ave., New Orleans, La.
Dr. Alice Potter, University of California Hospital, San Francisco, Calif.
Dr. W. Pierre Robert, 2449 Calder Ave., Beaumont, Texas
Dr. Burton Rosenholtz, 814 Lowry Medical Bldg., St. Paul, Minn.
Dr. William David Rothwell, 1612 Tremont St., Denver, Colo.
Dr. Joseph D. Russ, 3439 Prytania St., New Orleans, La. (in the Army)
Dr. Thomas J. Senese, 504 Broadway, Gary, Ind.
Dr. Miner W. Seymour, 370 E. Town St., Columbus, Ohio (in the Army)
Dr. Arthur L. Shafton, 1150 N. State St., Chicago, Ill.
Dr. Noel G. Shaw, 636 Church St., Evanston, Ill.
Dr. J. Sam Smith, 4 Catoma St., Montgomery, Ala.
Dr. Elaine Moore Thomas, 920 E. 59th St., Chicago, Ill.
Dr. John Martin Thomas, 301 N. 49th St., Omaha, Neb.
Dr. William Clifford Vance, 414 Med. Arts Bldg., Richmond, Ind. (in the Army)
Dr. Dorothy Fraser Wheeler, 608 T. W. Patterson Bldg., Fresno, Calif.
Dr. Edward Marion Wier, 1414 Pennsylvania Ave., Fort Worth, Texas
Dr. Alvin B. Williams, 311 S. 1st St., San Jose, Calif. (in the Navy)
Dr. Hillard Wood Willis, 2506 Ponce de Leon, Coral Gables, Fla.
Dr. David B. Witt, Central Regional Office La. State Dept. of Health, Alexandria, La. (attached to the Army)
Dr. Carl Witus, AAFAFS, Pampa, Texas (in the Army)
Dr. Louise A. Yeazell, University of California Hospital, San Francisco, Calif.
Dr. Edward William Zeman, Mesaba Clinic, Hibbing, Minn.
Dr. Helen Jane Zillmer, 781 N. Jefferson St., Milwaukee, Wis.

Book Reviews

Opportunities for the Preparation of Teachers in Health Education: A Survey of 20 Teachers' Colleges. Earl E. Kleinschmidt, M.D., D.P.H., Federal Security Agency, Office of Education, Bulletin No. 1, 1942, 117 pages, Superintendent of Documents, U. S. Government Printing Office, Washington, D. C. Price, 20 cents.

A detailed analysis of health instruction practices and curricula in twenty representative teacher-education institutions selected for the study is given. There is a brief but adequate general discussion of the status of health education in teachers' colleges and normal schools and the teachers' responsibility in health education. Finally, there is an enlightening review of the situation, and recommendations for improving services in health education, which is obviously inadequately prepared to offer a balanced program, shows the need for extensive changes in the future. These programs have received a marked stimulus and no doubt need to be reviewed immediately in this as well as other countries after peace is established. Pediatricians should, and will have, an important part in any such program.

McCULLOCH.

Infant Care. Department of Labor, Children's Bureau, Publication No. 8, ed. 4, 1942, 135 pages, Superintendent of Documents, U. S. Government Printing Office, Washington, D. C. Price, 10 cents (in coin or postal money order only).

The present revision is the work of Dr. Dorothy V. Whipple, with the cooperation of Dr. Marian M. Crane, both of the Division of Research in Child Development of the Children's Bureau. Dr. Ethel C. Dunham, Consultant in Pediatrics, wrote the section on the premature baby. The work was done under the general supervision of Dr. Katherine Bain, Director of the Division of Research in Child Development, and the manuscript was reviewed by the Bureau's advisory committee of pediatricians, who offered many helpful suggestions. The personnel of this committee represents the Section on Pediatrics of the American Medical Association, the American Pediatric Society, the American Academy of Pediatrics, and the one-time American Child Health Association, thus assuring the most important and authoritative pediatric interests available.

The book is intended to help parents in taking care of their babies. The information has been accumulated over the years and mellowed as the book has passed through successive editions and revisions but freshened also as further advances in the art of baby care have been made. It does not attempt to take the place of a doctor's regular supervision but should help parents understand what the doctor tells them. In the absence of pediatric guidance, it would be their main and best source of reliable information. With only trifling differences about minor details in special circumstances, this book can be unqualifiedly recommended to parents, nurses, and others interested in baby care. Indeed, this book could be the only one on this subject available without loss.

In comparing the present edition with all its predecessors, it is notable how the section on physical and mental growth and hygiene has been expanded and how the section on disease has been contracted. These changes are decidedly proper

and add greatly to the value of the book. The section on disease mentions only those which occur in infancy and presents the subject only from the point of view of prevention and early recognition. There is every evidence of careful thought and preparation as one reads the book critically.

McCULLOCH.

Tuberculosis Sanatorium Directory. National Tuberculosis Association, 1942, 185 pages. Price, $1.50.

Gives a geographic list of sanatoria, preventoria, and general hospitals having departments for tuberculosis patients; also shows the federal sanatoria, mental and isolation hospitals, and penal institutions making special provision for tuberculosis. One table indicates the number of tuberculosis institutions and the number of beds with exclusive or special provisions for children classified by states.

It is significant that the 12 per cent increase in number of beds for tuberculosis in continental United States since the publication of the last directory in 1938 has been in tax-supported institutions. Private or semiprivate institutions, on the other hand, have shown a loss of 5 per cent in beds, this loss being almost entirely in the strictly private institutions.

McCULLOCH.

1. **General Report of the Committee for the Study of the Care and Education of Physically Handicapped Children in the Public Schools of the City of New York.** Harold W. McCormick, Ed. D., et al., 1941, The Board of Education of the City of New York, 91 pages.
2. **Acoustically Handicapped Children.** Edmund Prince Fowler, Sr., M.D., 109 pages.
3. **Cardiac Classes and the Care of Cardiac Children.** Arthur C. DeGraff, M.D., 99 pages.
4. **Children With Speech Defects.** Walter O. Klingman, M.D., 61 pages.
5. **Children With Tuberculosis.** I. Ogden Woodruff, M.D., 17 pages.
6. **Epileptic Children.** George H. Hyslop, M.D., 61 pages.
7. **Open Air Classes and the Care of Below Par Children.** I. Ogden Woodruff, 83 pages.
8. **Orthopedically Handicapped Children.** Benjamin P. Farrell, M.D., 141 pages.
9. **Psychological Considerations in the Education of the Handicapped.** Ira S. Wile, M.D.
10. **The Education of Children in Hospitals and Convalescent Homes.** Marshall C. Pease, M.D., 57 pages.
11. **Visually Handicapped Children.** Conrad Berens, M.D.

The general report has been prepared on the basis of all the studies of the Committee and presents an overview of the whole program for physically handicapped children in New York City. The report of the Subcommittee is prepared separately, including in each instance a summary of findings and recommendations.

The first and most important of the general conclusions drawn from this survey is that the medical and educational programs for the physically handicapped, which have developed in the public schools over a period of years, are no longer in harmony with current medical educational advances. If this is true in New York City, where the program has been under way for a long time and on a large scale, then the program in other communities probably needs, also, a severe overhauling and reconstruction. In a postwar world where great attention will need be given children of all classes, normal as well as physically handicapped, it is high time that constructive and adequate plans be made. The report, appearing at the same time

as the report of the Astoria Demonstration Study,* should arouse the interest of the pediatrician within whose province lies much of the responsibility of future developments. It is interesting to note the names of only two pediatricians on the list of those who participated in these studies, and no pediatric organization is mentioned as assisting the Committee.

McCULLOCH.

Athletic Injuries: Prevention, Diagnosis and Treatment. Augustus Thorndike, M.D., 1942, Cambridge, Mass., Lea & Febiger, ed. 2, 216 pages. Price, $3.00.

The inclusion of certain developments of the physiology of physical fitness constitutes the important additions to this edition. This new material should make the book even more useful to pediatricians and, with the suggested literature in the bibliography, should supply him with valuable information concerning the fitness of his children to undertake high school and college physical training and athletics. This is an important problem in the minds of many parents, with many phases to be considered and solved. Many of the answers are to be found in this book.

McCULLOCH.

Nutrition and Chemical Growth in Childhood. Vol. 1. Evaluation. Macy, Icie G., Ph.D., Springfield, Ill., 1942, Charles C Thomas, 432 pages. Price, $5.00.

This is the first of two volumes written by the author to summarize and interpret the results of extensive investigations carried out by her and her collaborators during the past two decades under the auspices of the Merrill Palmer School, the Children's Hospital of Michigan, and the Children's Fund of Michigan.

Volume I, with the subtitle Evaluation, presents the scientific material accumulated to date. It includes also a critical review of all procedures and special methods used in collecting and evaluating the data. Nearly every phase of normal childhood nutrition capable of being measured appears to have been covered by the investigations reported. While the major theme of the monograph relates to metabolic balance studies, such accessory subjects as appetite, digestion, gastrointestinal motility, energy metabolism, and even some phases of normal hematology are considered in their relationship to the underlying processes of chemical growth in the human subject. The factual data presented comprise a summary of experimental results reported in more than one hundred original papers from the Detroit laboratories. Much of the scientific material is presented in condensed or tabular form in 122 tables and many self-explanatory charts. A list of nearly 400 complete references to the general literature on the subject adds value to the volume. The text of the latter is written in a clear, easy style, and the illustrations are well selected. It is the most concise and comprehensive treatise on this particular subject known to the reviewer. As a handbook, it will be found especially useful to pediatricians and nutritionists who wish to carry out metabolic studies in either normal or sick children.

McQUARRIE.

*Solving School Health Problems. Dorothy B. Nyswander, The Commonwealth Fund, New York, 1942.